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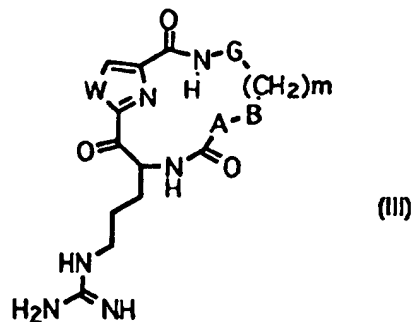
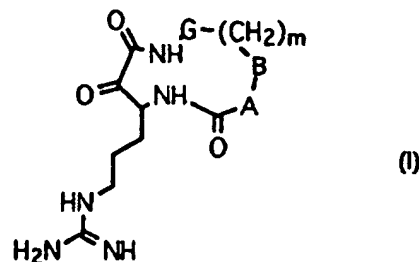
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(54) Title: MACROCYCLIC PEPTIDES USEFUL IN THE TREATMENT OF THROMBIN RELATED DISORDERS

(57) Abstract

Compounds of Formula (I) and Formula (III) which are useful
in the treatment of thrombin and trypsin related disorders.



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MACROCYCLIC PEPTIDES USEFUL IN THE TREATMENT OF THROMBIN RELATED DISORDERS

This invention relates a series of macrocyclic peptides, intermediates
5 used in their manufacture and pharmaceutical compositions containing
them. The compounds are inhibitors of serine proteases, particularly α -
thrombin and may be used in a variety of thrombin related disorders such as
venous thrombosis and arterial thrombosis.

10 BACKGROUND OF THE INVENTION

With a rapidly aging population, diseases of the vascular system are
of great concern to our society. Arterial thrombosis is the major cause of
death in the form of heart attacks and strokes, while venous thrombosis is
15 associated with pulmonary embolism which occurs after surgery or extended
periods of inactivity.

Thrombin is a multifunctional serine protease whose role in
thrombosis and hemostasis has been documented by a number of sources
(See generally, Tapparelli, et al, *TIPS* 1993, 14, 366-76). Thrombin acts as
20 a procoagulant through proteolytic cleavage of fibrinogen to form fibrin and
as an anticoagulant through activation of the protein C pathway (followed by
inactivation of coagulation factors V and VIII.) The concentration of active
thrombin is limited by a number of feedback mechanisms involving
endogenous factors and proteins. In addition to protein C, antithrombin III is
25 another regulating protein which forms a complex with endogenous heparin.
This complex binds to active thrombin, thus inactivating it.

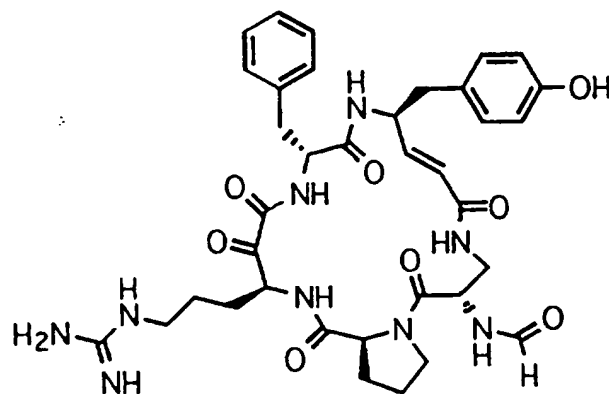
Current anticoagulant therapy consists of three classes of
compounds: heparins, coumarins and low molecular weight heparins.
These drugs act indirectly to limit the concentration of active thrombin.
30 Heparins and low molecular weight heparins interact with antithrombin III
and the coumarins inhibit a number of vitamin K dependent coagulation
factors. Although these drugs are prescribed for diseases associated with
venous thrombosis and arterial thrombosis, their use is limited. They have a
number of side effects, a slow onset of action and only the coumarins are
35 orally active (warfarin and dicumarol).

Indirect thrombin inhibitors have been shown to be less effective at
controlling associated diseases than direct thrombin inhibitors. Thus the
search for orally active direct thrombin inhibitors is underway in a number of

laboratories. These efforts have produced a number of acyclic peptidyl compounds which directly inhibit thrombin. PPACK, argatroban, (D)-NAPAP, hirulog-1 and DUP 714 are examples of these inhibitors. Many of these compounds lack useful oral activity, and many have a poor selectivity for thrombin versus other serine proteases. Therefore, a need remains for new direct thrombin inhibitors.

When compared to acyclic peptides, cyclic peptides have a number of structural features that have been linked to changes in the biological activity of simple peptides. Due to the absence of polar end groups and a relatively rigid structure, cyclic peptides are hypothesized to be more membrane permeable and less susceptible to peptidases. Potentially one could incorporate the structure of simple peptides, within rigid, non-polar macrocyclic framework, to produce active bioavailable compounds.

Cyclotheonamide A (CtA) is a cyclic peptide which was isolated from
15 Theonella.sp, a marine sponge. It inhibits a variety of serine proteases
particularly thrombin and trypsin.

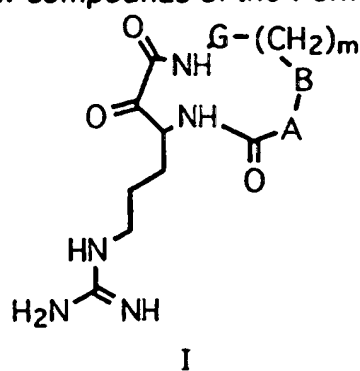


cyclotheonamide A (CtA)

20

Although this molecule inhibits thrombin (K_i ca. 1-2 nM), it is a scarce natural product which is difficult to extract from its natural source. In addition, CtA is not an optimal candidate for treating thrombin-related disorders as its selectivity for thrombin over trypsin does not favor thrombin. The invention described below claims a novel macrocyclic peptides that inhibit thrombin at nanomolar levels and exhibit reasonable selectivity for thrombin over trypsin.

The invention relates to new compounds of the Formula I

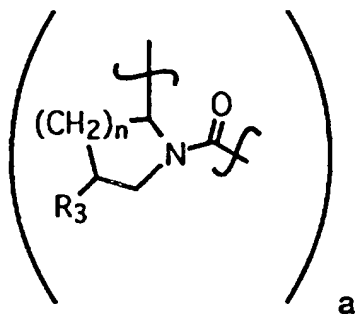


wherein:

5

m is 2 to 12;

A is



10

where the amido carbonyl is bound to B and the α aminomethine is bound to the depicted ring carbonyl,

15

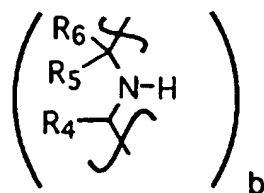
R₃ is hydrogen, hydroxy or C₁₋₅alkoxy,

n is 1 or 2 and

a is 0 or 1;

20

B is



where the amido carbonyl of B is bound to the depicted ring methylenes and the methine is bound to A,

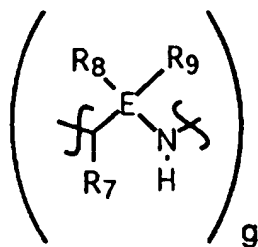
5 R_4 is selected from the group consisting of any of hydrogen, C_{1-5} alkyl, carboxy C_{1-5} alkyl, phenyl, substituted phenyl (where the phenyl substituents are C_{1-5} alkyl, carboxy C_{1-5} alkoxycarbonyl, carboxamido, amino, C_{1-5} alkylamino, hydroxy, C_{1-5} alkylcarbonylamino, C_{1-5} alkoxy, fluorine, bromine
10 or chlorine), phenyl C_{1-5} alkyl, substituted phenyl C_{1-5} alkyl (where the phenyl substituents are C_{1-5} alkyl, carboxy C_{1-5} alkoxycarbonyl, carboxamido, amino, C_{1-5} alkylamino, hydroxy, C_{1-5} alkylcarbonylamino, C_{1-5} alkoxy, fluorine bromine or chlorine), 3-pyridyl C_{1-5} alkyl, 4-pyridyl C_{1-5} alkyl,
15 diphenyl C_{1-2} alkyl, naphthyl or substituted naphthyl (where the naphthyl substituents are C_{1-5} alkyl, carboxy C_{1-5} alkoxycarbonyl, carboxamido, amino, C_{1-5} alkylamino, hydroxy, C_{1-5} alkylcarbonylamino, C_{1-5} alkoxy, fluorine bromine or chlorine),

20 R_5 and R_6 are each hydrogen or taken together with the carbon to which each is attached to form a carbonyl, and

b is 0 or 1;

25

G is



30 where the amine of G is bound to the ring methylenes and the methine is bound to the depicted amide,

R_7 is independently selected from the group consisting of hydrogen, C_{1-5} alkyl, carboxy C_{1-5} alkyl, phenyl, substituted phenyl (where the

phenyl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅ alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine), phenylC₁₋₅alkyl, substituted phenylC₁₋₅alkyl (where the phenyl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine), 3-pyridylC₁₋₅alkyl, 4-pyridylC₁₋₅alkyl, diphenylC₁₋₂alkyl, and naphthyl, substituted naphthyl (where the naphthyl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine),

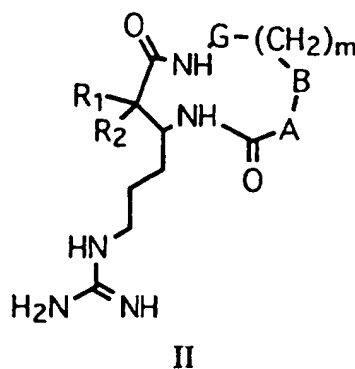
E is carbon or $C(CH_2)_q$, where q is 0 to 12, with the proviso that the sum of q and m cannot exceed 25.

15 R₈ and R₉ are hydrogen or taken together with the carbon of E to form a carbonyl, and

g is 0 or 1;

20 and pharmaceutically acceptable salts thereof.

25 An additional aspect of the invention relates to novel compounds of the Formula II which are intermediates in the synthesis of compounds for the Formula I.



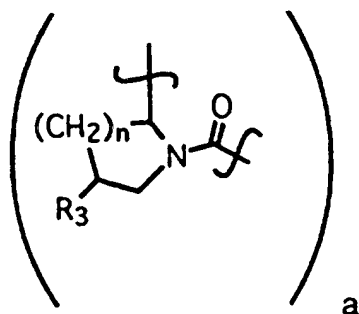
wherein:
30 R₁ is hydroxy;

R₂ is hydrogen;

m is 2 to 12;

A is

5



where the amido carbonyl is bound to B and the α aminomethine is bound to the depicted ring carbonyl,

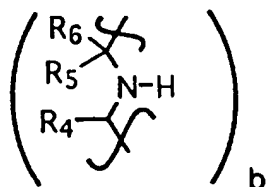
10

R_3 is hydrogen or C_{1-5} alkoxy,

n is 1 or 2, and

15 a is 0 or 1;

B is



20

where the amido carbonyl of B is bound to the depicted ring methylenes and the methine is bound to A,

25 R_4 is selected from the group consisting of hydrogen, C_{1-5} alkyl, carboxy C_{1-5} alkyl, phenyl, substituted phenyl (where the phenyl substituents are C_{1-5} alkyl, carboxy C_{1-5} alkoxycarbonyl, carboxamido, amino, C_{1-5} alkylamino, hydroxy, C_{1-5} alkylcarbonylamino, C_{1-5} alkoxy, fluorine bromine or chlorine), phenyl C_{1-5} alkyl, substituted phenyl C_{1-5} alkyl (where the phenyl

5

substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine), 3-pyridylC₁₋₅alkyl, 4-pyridylC₁₋₅alkyl, diphenylC₁₋₂alkyl, naphthyl or substituted naphthyl (where the naphthyl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine, bromine or chlorine),

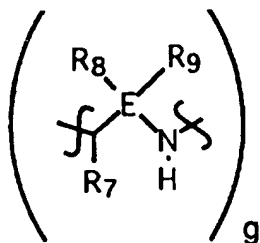
10

R₅ and R₆ are each hydrogen or taken together with the carbon to which each is attached to form a carbonyl,

b is 0 or 1;

15

G is



20

where the amine of G is bound to the ring methylenes and the methine is bound to the depicted amide,

25

R₇ is selected from the group consisting of hydrogen, C₁₋₅alkyl, carboxyC₁₋₅alkyl, phenyl, substituted phenyl (where the phenyl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine), phenylC₁₋₅alkyl, substituted phenylC₁₋₅alkyl (where the phenyl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine), 3-pyridylC₁₋₅alkyl, 4-pyridylC₁₋₅alkyl, diphenylC₁₋₂alkyl, naphthyl or substituted naphthyl (where the naphthyl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl,

30

carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine, bromine or chlorine),

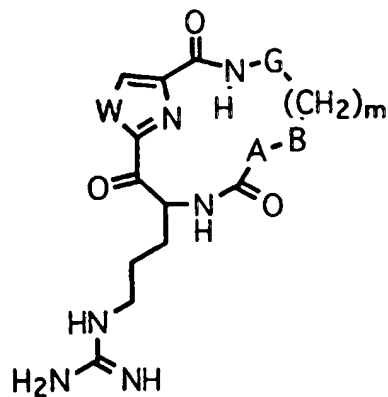
- 5 E is carbon or C(CH₂)_q, where q is 0 to 12, with the proviso that the sum of q and m cannot exceed 25,

R₈ and R₉ are each hydrogen or taken together with the carbon of E to form a carbonyl,

- 10 g is 0 or 1;

or pharmaceutically acceptable salts thereof.

Yet another aspect of the invention relates to novel thrombin inhibitors of the Formula III.



III

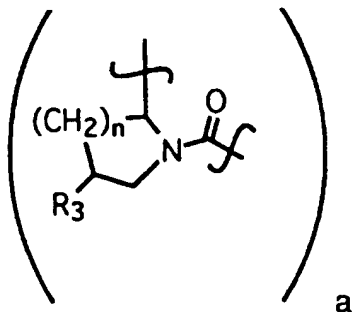
5 wherein:

m is 2 to 12;

W is nitrogen, sulfur or oxygen;

10

A is



15

where the amido carbonyl is bound to B and the α aminomethine is bound to the depicted ring carbonyl,

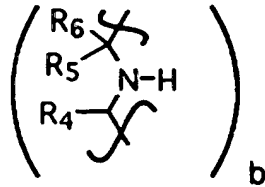
R₃ is hydrogen, hydroxy or C₁₋₅alkoxy,

20

n is 1 or 2;

a is 0 or 1;

B is



5 where the amido carbonyl of B is bound to the depicted ring methylenes and the methine is bound to A,

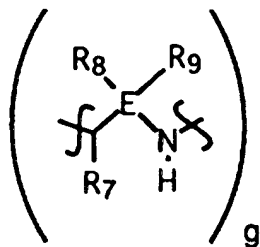
10 R_4 is selected from the group consisting of hydrogen, C_{1-5} alkyl, carboxy C_{1-5} alkyl, phenyl, substituted phenyl (where the phenyl substituents are C_{1-5} alkyl, carboxy C_{1-5} alkoxycarbonyl, carboxamido, amino, C_{1-5} alkylamino, hydroxy, C_{1-5} alkylcarbonylamino, C_{1-5} alkoxy, fluorine bromine or chlorine), phenyl C_{1-5} alkyl, substituted phenyl C_{1-5} alkyl (where the phenyl substituents are C_{1-5} alkyl, carboxy C_{1-5} alkoxycarbonyl, carboxamido, amino, C_{1-5} alkylamino, hydroxy, C_{1-5} alkylcarbonylamino, C_{1-5} alkoxy, fluorine bromine or chlorine), 3-pyridyl C_{1-5} alkyl, 4-pyridyl C_{1-5} alkyl, diphenyl C_{1-2} alkyl, naphthyl or substituted naphthyl (where the naphthyl substituents are C_{1-5} alkyl, carboxy C_{1-5} alkoxycarbonyl, carboxamido, amino, C_{1-5} alkylamino, hydroxy, C_{1-5} alkylcarbonylamino, C_{1-5} alkoxy, fluorine bromine or chlorine),

20 R_5 and R_6 are each hydrogen or taken together with the carbon to which they are attached to form a carbonyl,

25

b is 0 or 1;

G is



where the amine of G is bound to the ring methylenes and the methine is bound to the depicted amide,

R₇ is independently selected from the group consisting of hydrogen,

C₁₋₅alkyl, carboxyC₁₋₅alkyl, phenyl, substituted phenyl (where the phenyl substituents are C₁₋₅alkyl, carboxy

C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine), phenylC₁₋₅alkyl, substituted phenylC₁₋₅alkyl (where the phenyl substituents are C₁₋₅alkyl, carboxy

C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine), 3-pyridylC₁₋₅alkyl, 4-pyridylC₁₋₅alkyl, diphenylC₁₋₂alkyl, naphthyl or substituted naphthyl (where the naphthyl substituents are C₁₋₅alkyl, carboxy

C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine),

E is carbon or C(CH₂)_q, where q is 0 to 12, with the proviso that the sum of q and m cannot exceed 25,

R₈ and R₉ are each hydrogen or taken together with the carbon of E to form a carbonyl,

g is 0 or 1;

or pharmaceutically acceptable salts thereof.

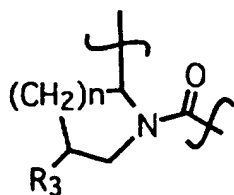
The terms used in describing the invention are commonly used and known to those skilled in the art. However, the terms that could have other meanings are defined. "Independently" means that when there are more than one substituent, the substituents may be the same or different. The term "alkyl" refers to straight, cyclic and branched-chain alkyl groups and "alkoxy" refers to O-alkyl where alkyl is as defined supra. "CBZ" refers to benzyloxycarbonyl. "BOC" refers to t-butoxycarbonyl and "Ts" refers to toluenesulfonyl. "DCC" refers to 1,3-dicyclohexylcarbodiimide, "DMAP" refers to 4-N,N-dimethylaminopyridine and "HOBT" refers to 1-hydroxybenzotriazole hydrate. "FMoc" refers to N-(9-fluorenylmethoxycarbonyl). Amino acid refers to compounds where the amino group and the carboxy group are on different carbon atoms. The term α -amino acid, refers to compounds where both the carboxy and the amino group are attached to the same carbon atom. The stereochemistry of this carbon is indicated by the terms "D and L" where D indicates right-handed chirality.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of the invention may be prepared by a number of synthetic schemes, where the macrocyclic ring members A, B, and G dictate the appropriate synthesis. The starting protected mono and di-peptides are either known or readily synthesized by standard techniques known in the art. See Bodansky, M. *Practice of Peptide Synthesis*; Springer Verlag, 1984. All syntheses include a series of peptide coupling reactions, where the macrocycle is built, oxidized and deprotected.

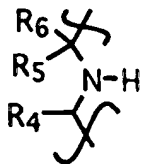
As illustrated, Scheme I may be used to prepare a compound of Formula I where m is 7;

A is



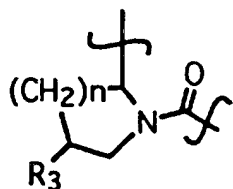
where R_3 is hydrogen and n is 1;

B is



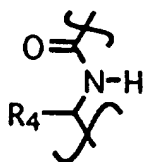
- 5 where R₄ is 2-methyl-1-propyl and R₅ is taken together with R₆ to form a carbonyl. A known N-protected α-amino acid I_a, is coupled at room temperature to a known C-protected amino acid I_b, using HOBT/DCC in an inert solvent, such as DMF, CH₃CN or THF, over 5-24 h. Although HOBT/DCC is the preferred coupling agent other agents can be used and
- 10 include: BOP, BOP-Cl and PyBrOP. The protecting groups are chosen in order to permit selective removal, where the favored protecting groups are CBZ for nitrogen and *t*-butoxycarbonyl for carboxy. However, other well known protecting groups may be substituted and are described in Green, Theodora *Protecting Groups in Organic Synthesis*; John Wiley & Sons, New
- 15 York, 1981. As illustrated the CBZ group is removed by hydrogenation at approximately 20 psig using Pd(OH)₂/C as a catalyst. However, other conditions may be used such as catalytic transfer hydrogenation using Pd/C and formic acid. The resulting C-protected di-peptide I_c, is coupled to an N-protected aliphatic amino acid, I_d, followed by removal of the N-protecting
- 20 group to give amine I_e. As illustrated, the CBZ serves as the N-protecting group and Pd/(OH)₂ is the hydrogenation catalyst. However either the protecting group or the reaction conditions may be modified as previously described. Intermediate I_e is coupled to 6-[[imino[4-methylbenzenesulfonyl]-amino]methyl]amino]-2-(R,S)-[[2-(trimethylsilyl)ethoxy]methoxy]-3(S)-
- 25 [9-phenylmethoxycarbonyl)-amino]hexanoic acid, (Maryanoff *et al.* *Journal of the American Chemical Society* 1995, 117, 1225-39) using HOBT/DCC at room temperature for 4-24 h in an inert solvent and deprotected with Pd(OH)₂ to give the arginine derivative I_f. The *t*-butoxycarbonyl and SEM protecting groups are removed with TFA and the resulting intermediate is
- 30 coupled at room temperature with BOP-Cl and DMAP in an inert solvent such as CH₂Cl₂ to give the hydroxy macrocyclic derivative I_g. Compound I_g is oxidized using the Dess-Martin periodinane in an anhydrous aprotic solvent and deprotected using HF in the presence of a carbocation scavenger such as anisole, thioanisole, pentamethylbenzene,
- 35 dimethylsulfide or cresol to give a compound of Formula I.

This scheme may be used to form the compounds of the invention where m is 2-12, A is

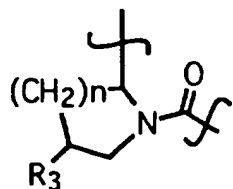


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where n is 1 or 2 and R_3 is hydrogen or C_{1-5} alkoxy, and B is

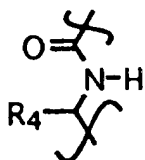


- 10 where R_4 is hydrogen, C_{1-5} alkyl, phenyl, substituted phenyl (where the phenyl substituents are C_{1-5} alkyl, carboxy C_{1-5} alkoxycarbonyl, carboxamido, amino, C_{1-5} alkylamino, hydroxy, C_{1-5} alkylcarbonylamino, C_{1-5} alkoxy, fluorine bromine or chlorine), phenyl C_{1-5} alkyl, substituted phenyl C_{1-5} alkyl (where the phenyl substituents are C_{1-5} alkyl, carboxy
- 15 C_{1-5} alkoxycarbonyl, carboxamido, amino, C_{1-5} alkylamino, hydroxy, C_{1-5} alkylcarbonylamino, C_{1-5} alkoxy, fluorine bromine or chlorine), 3-pyridyl C_{1-5} alkyl, 4-pyridyl C_{1-5} alkyl, naphthyl, substituted naphthyl or diphenyl C_{1-2} alkyl. For example to prepare compounds where m is 2-12, the illustrated reactant Id, 8-(*N*-benzyloxycarbonyl)aminooctanoic acid, is
- 20 replaced with an analog of " m " methylenes such as 6-(*N*-benzyloxycarbonyl)aminohexanoic acid. To prepare a compound where A is



25

R_3 is hydrogen and n is 2, simply replace Ib, D-Pro-O-*t*-Bu, with D-pipecolinic acid -*t*-butyl ester To prepare a compound where B is

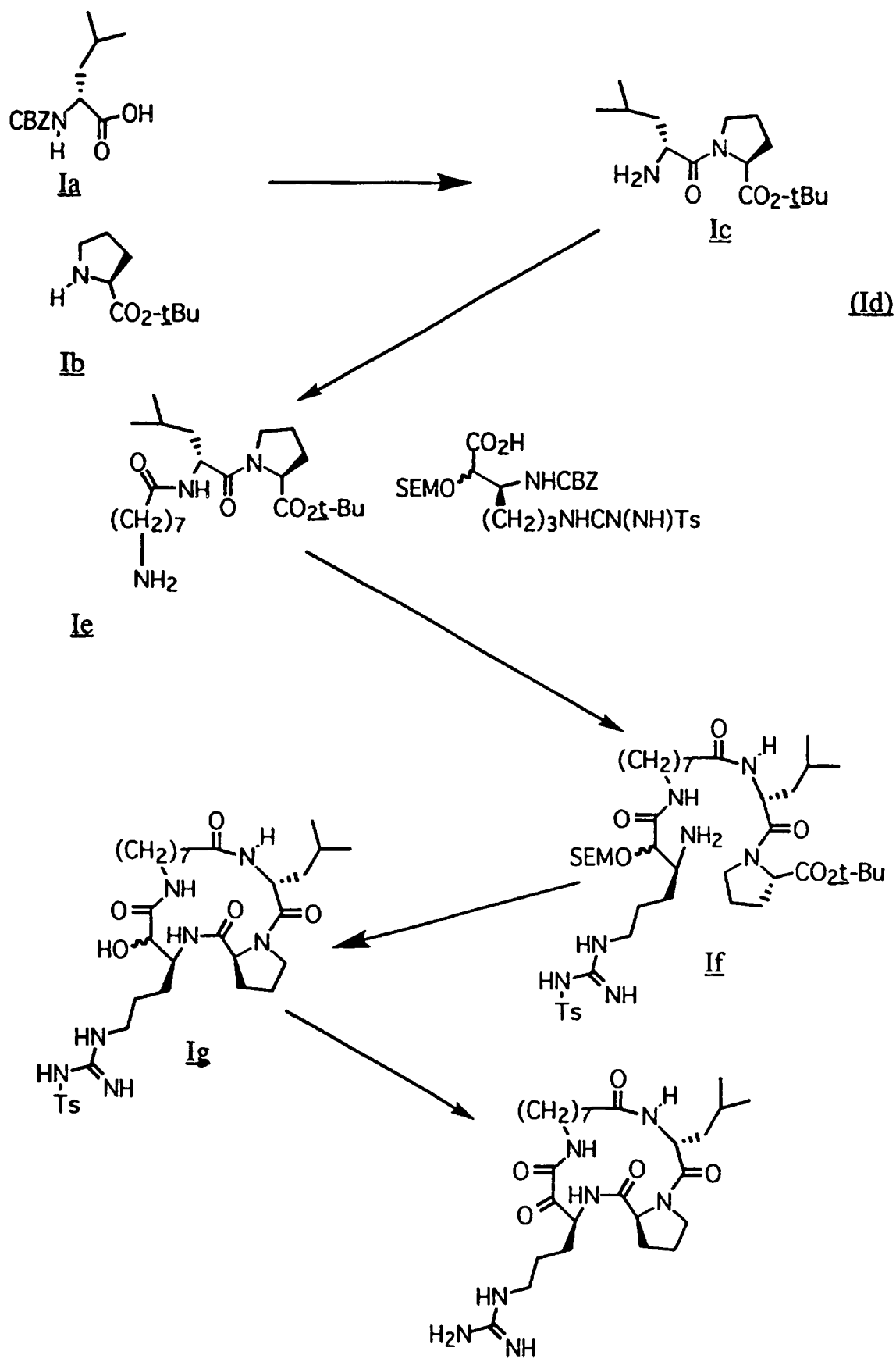


5

and R_4 is 3-pyridylmethyl, replace Ia N-BOC-D-leucine with N-BOC-D-3-pyridyl-alanine. When active aromatic substituents are desired such as hydroxy, amino or carboxy, those compounds may be prepared as protected derivatives where the protecting groups well known in the art are described in Green, Theodora *Protecting Groups in Organic Synthesis*; John Wiley & Sons, New York, 1981. For example to prepare a compound where R_4 is 4-hydroxybenzyl, a *t*-butyldimethylsilyl group is used as protecting group and removed with HF in the last step of the scheme.

10

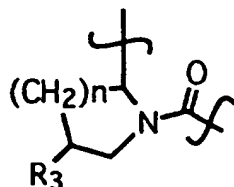
SCHEME I



Another method of synthesis, illustrated by Scheme II, may be used to prepare a compound of Formula I where m is 4;

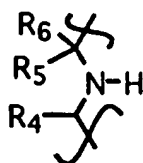
A is

5



where R_3 is hydrogen and n is 1;

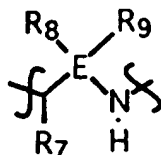
10 B is



where R_4 is benzyl and R_5 is taken together with R_6 to form a carbonyl; and

15

G is

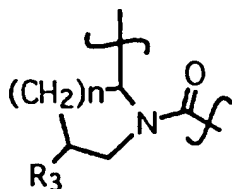


20 where E, R_8 and R_9 are taken together to form a carbonyl and R_7 is 4-chlorobenzyl.

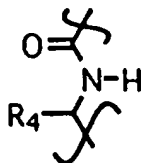
A known N-protected - α -amino acid IIa, is coupled at room temperature to a known C-protected amino acid IIb, using HOBT/DCC in an inert solvent, such as DMF, CH_3CN or THF, over 5-24 h. Although HOBT/DCC is the preferred coupling agent other agents may be used and include: BOP, BOP-Cl and PyBrOP. The protecting groups are chosen in order to permit selective removal, where the favored protecting groups are CBZ for nitrogen and *t*-butoxycarbonyl for carboxy. However, other protecting groups well known in the art may be substituted and are

described in Green, Theodora, *Protecting Groups in Organic Synthesis*; John Wiley & Sons, New York, 1981. As illustrated the *t*-butoxycarbonyl group is removed with TFA to give the *N*-protected di-peptide **IIc**. This intermediate is coupled to an *C*-protected di-peptide **IIId**, followed by removal of the *N*-protecting group to give amine **IIe**. As illustrated the CBZ serves as the *N*-protecting group and Pd/(OH)₂ is the hydrogenation catalyst. However either the protecting group or the reaction conditions may be modified as previously described. Intermediate **IIe** is coupled to 6-[[imino[4-methylbenzenesulfonyl)-amino]methyl]amino]-2-(R,S)-[[2-(trimethylsilyl)ethoxy]methoxy]-3(S)-[9-phenylmethoxycarbonyl)-amino]hexanoic acid, (Maryanoff *et al.* *Journal of the American Chemical Society* 1995, 117, 1225-39) using HOBt/DCC at room temperature for 4-24 h in an inert solvent and deprotected with Pd(OH)₂ to give the arginine derivative **IIIf**. The *t*-butoxycarbonyl and SEM protecting groups are removed with TFA and the resulting intermediate is coupled at room temperature with BOP-Cl and DMAP in an inert solvent such as CH₂Cl₂ to give the hydroxy macrocyclic derivative **IIg**. Compound **IIg** is oxidized using the Dess-Martin periodinane in an anhydrous aprotic solvent and deprotected using HF in the presence of a carbocation scavenger to give a compound of Formula I.

This scheme may be used to form the compounds of the invention where m is 2-12, A is

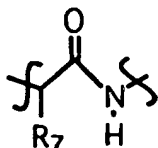


where R₃ is hydrogen or C₁₋₅alkoxy, B is

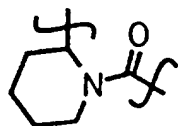


where R₄ is hydrogen, C₁₋₅alkyl, phenyl, substituted phenyl (where the phenyl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino,

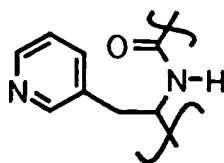
- C₁₋₅alkoxy, fluorine bromine or chlorine), phenylC₁₋₅alkyl, substituted phenylC₁₋₅alkyl (where the phenyl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine), 3-pyridylC₁₋₅alkyl, 4-pyridylC₁₋₅alkyl or diphenylC₁₋₂alkyl, and G is



- where R₇ is hydrogen, C₁₋₅alkyl, phenyl, substituted phenyl (where the phenyl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine), phenylC₁₋₅alkyl, substituted phenylC₁₋₅alkyl (where the phenyl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine), 3-pyridylC₁₋₅alkyl, 4-pyridylC₁₋₅alkyl, naphthyl or diphenylC₁₋₂alkyl. For example to prepare compounds where m is 2-12, the illustrated reactant IIb, 5-aminopentanoic acid -t-butyl ester is replaced with an analog of "m" methylenes such as 7-aminoheptanoic acid -t-butyl ester To prepare a compound where A is

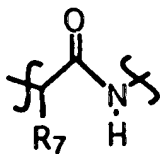


and B is



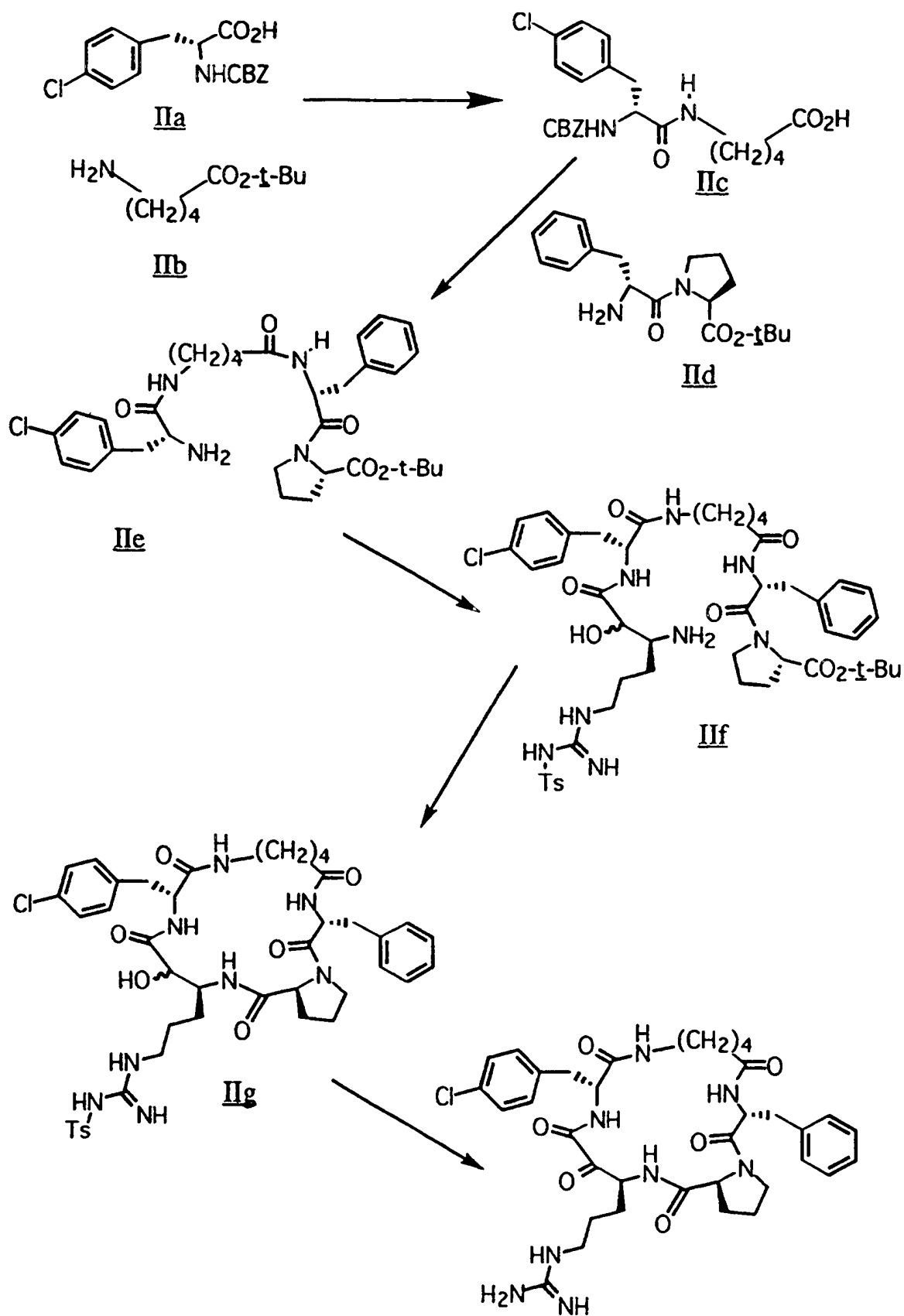
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replace the illustrated reactant IIId with 3-pyridylalanine-pipecolinic acid (O-tBu) A compound where G is



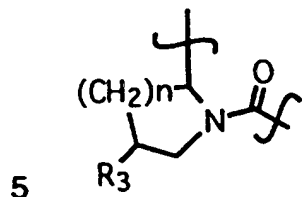
- and R_7 is butyl can be prepared by replacing IIa with N-BOC-D-norleucine. When the aromatic substituents hydroxy, amino or carboxy are desired, those compounds may be prepared as protected derivatives where the protecting groups well known in the art are described in Green, Theodora *Protecting Groups in Organic Synthesis*; John Wiley & Sons, New York, 1981. For example to prepare compound where R_4 or R_7 is 4-aminobenzyl, an allyloxycarbonyl group is used as protecting group and removed with tetrakis(triphenylphosphine)palladium(0) at the end of the scheme.
- 5

SCHEME II



Yet another method, illustrated by Scheme III, is used to prepare a compound of Formula I where m is 3;

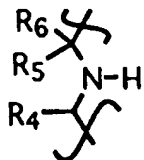
A is



where R₃ is hydrogen and n is 2;

B is

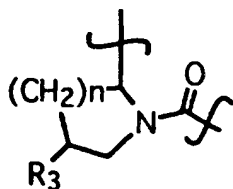
10



where R₄ is benzyl and both R₅ as well as R₆ are hydrogen. A known N-protected aldehyde IIIa, is reductively aminated at room temperature to a known C-protected amino acid IIIb, using NaB(OAc)₃H in an inert solvent, such as CH₂Cl₂ or (CH₂)₂Cl₂, over 2-16 h. The protecting groups are chosen in order to permit selective removal, where the favored protecting groups are Fmoc for nitrogen and t-butoxycarbonyl for carboxy. However, other protecting groups may be substituted as previously discussed. The free amine of the resulting product IIIc is protected as the CBZ and the Fmoc group of the other amine is cleaved with an anhydrous base such as piperidine to give IIId. Intermediate IIId is coupled to 6-[[imino[4-methylbenzenesulfonyl)-amino]methyl]amino]-2-(R,S)-[[2-(trimethylsilyl)ethoxy]methoxy]-3(S)-[9-fluorenylmethoxycarbonyl)-amino]hexanoic acid, (Maryanoff *et al.* *Journal of the American Chemical Society* 1995, 117, 1225-39) using HOBt/DCC at room temperature for 4-24 h in an inert solvent and deprotected with Pd(OH)₂ to give the arginine derivative IIIe. The Fmoc group is removed with an organic base and the t-butoxycarbonyl and SEM protecting groups are removed with TFA. The resulting intermediate is coupled at room temperature with BOP-Cl and DMAP in an inert solvent such as CH₂Cl₂ to give the hydroxy macrocyclic derivative IIIf. Compound IIIf is oxidized using the Dess-Martin periodinane

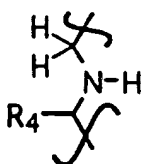
in an anhydrous aprotic solvent and deprotected using HF in the presence of a carbocation scavenger to give a compound of Formula I.

This Scheme III may be used to form the compounds of the invention
 5 where m is 2-12, A is

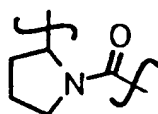


where R₃ hydrogen or C₁₋₅alkoxy and n is 1 or 2, and B is

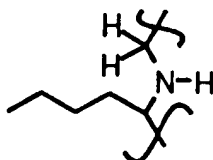
10



where R₄ is hydrogen, C₁₋₅alkyl, phenyl, substituted phenyl (where the
 15 phenyl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl,
 carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino,
 C₁₋₅alkoxy, fluorine bromine or chlorine), 3-pyridylC₁₋₅alkyl,
 4-pyridylC₁₋₅alkyl or diphenylC₁₋₂alkyl. For example to prepare compounds
 where m is 2-12, the illustrated reactant IIIa, is replaced with an analog of
 "m" methylenes such as 5-(N-9-
 20 fluorenylmethoxycarbonyl)aminopentaldehyde To prepare a compound
 where A is

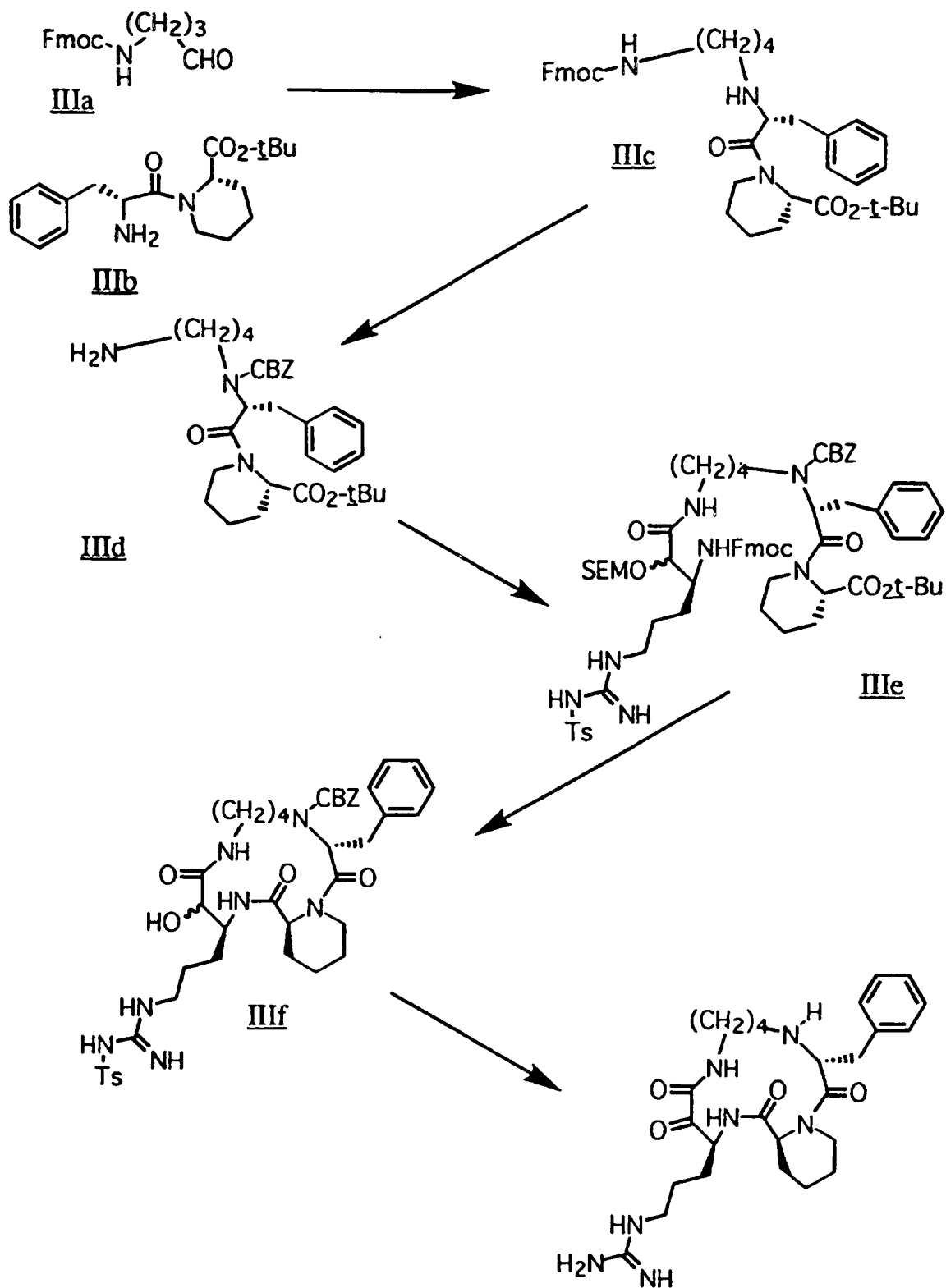


25 and B is



- replace the illustrated reactant **IIIb** with norleucine-proline-(O-t-Bu). When active aromatic substituents are desired such as hydroxy, amino or carboxy, those compounds may be prepared as protected derivatives where the
- 5 protecting groups well known in the art are described in Green, Theodora *Protecting Groups in Organic Synthesis*; John Wiley & Sons, New York, 1981. For example to prepare compound where R₄ is 4-carboxybenzyl, an methylester is used as protecting group and removed with aqueous LiOH prior to oxidation with Dess Martin periodiane.

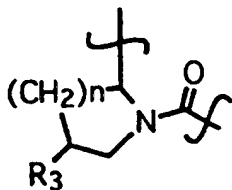
SCHEME III



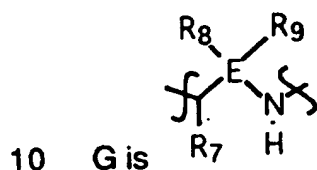
Another method of synthesis is illustrated by Scheme IV may be used to prepare a compound of Formula I where m is 5;

A is

5



where R₃ is hydrogen and n is 1; and



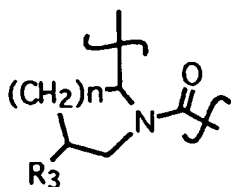
where E, R₈ and R₉ are taken together to form a carbonyl and R₇ is phenyl.

A known N-protected amino acid IVa, is coupled at room temperature to a known C-protected amino acid IVb, using HOBT/DCC in an inert solvent, such as DMF, CH₃CN or THF, over 5-24 h. Although HOBT/DCC is the preferred coupling agent other agents be used and include: BOP, BOP-Cl and PyBrOP. The preferred protecting groups are CBZ for nitrogen and *t*-butoxycarbonyl for carboxy; however, other protecting groups may be substituted as discussed previously. As illustrated the *t*-butoxycarbonyl group is removed with TFA to give the N-protected di-peptide IVc. This intermediate is coupled to an C-protected di-peptide IVd, followed by removal of the N-protecting group to give amine IVe. As illustrated the CBZ serves as the N-protecting group and Pd/(OH)₂ is the hydrogenation catalyst. However either the protecting group or the reaction conditions may be modified as previously described. Intermediate IVe is coupled to 6-[[imino[4-methylbenzenesulfonyl)-amino]methyl]amino]-2-(R,S)-[[2-(trimethylsilyl)ethoxy]methoxy]-3(S)-[9-phenylmethoxycarbonyl)-amino]hexanoic acid, (Maryanoff *et al.* *Journal of the American Chemical Society* 1995, 117, 1225-39) using HOBT/DCC at room temperature for 4-24 h in an inert solvent and deprotected with Pd(OH)₂ to give the arginine derivative IVf. The *t*-butoxycarbonyl and SEM protecting groups are

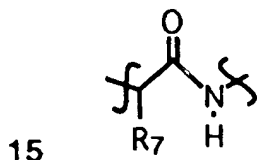
- removed with TFA and the resulting intermediate is coupled at room temperature with BOP-Cl and DMAP in an inert solvent such as CH_2Cl_2 to give the hydroxy macrocyclic derivative IVg. Compound IVg is oxidized using periodinane in an anhydrous aprotic solvent and deprotected using
- 5 HF in the presence of a carbocation scavenger to give a compound of Formula I.

This Scheme IV may be used to form the compounds of the invention where m is 2-12, A is

10

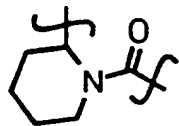


and G is

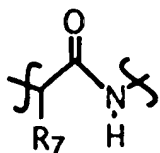


15

- where R_7 is hydrogen, C_{1-5} alkyl, phenyl, substituted phenyl (where the phenyl substituents are C_{1-5} alkyl, carboxy C_{1-5} alkoxycarbonyl, carboxamido, amino, C_{1-5} alkylamino, hydroxy, C_{1-5} alkylcarbonylamino,
- 20 C_{1-5} alkoxy, fluorine bromine or chlorine), phenyl C_{1-5} alkyl, substituted phenyl C_{1-5} alkyl (where the phenyl substituents are C_{1-5} alkyl, carboxy C_{1-5} alkoxycarbonyl, carboxamido, amino, C_{1-5} alkylamino, hydroxy, C_{1-5} alkylcarbonylamino, C_{1-5} alkoxy, fluorine bromine or chlorine), 3-pyridyl C_{1-5} alkyl, 4-pyridyl C_{1-5} alkyl naphthyl or diphenyl C_{1-2} alkyl. For
- 25 example to prepare compounds where m is 2-12, the illustrated reactant IVa, 6-(*N*-CBZ)aminohexanoic acid is replaced with an analog of "m" methylenes such as 7-(*N*-CBZ)aminoheptanoic acid. To prepare a compound where A is



replace the illustrated reactant IVb with D-pipecolinic acid t-butyl ester. A compound where G is

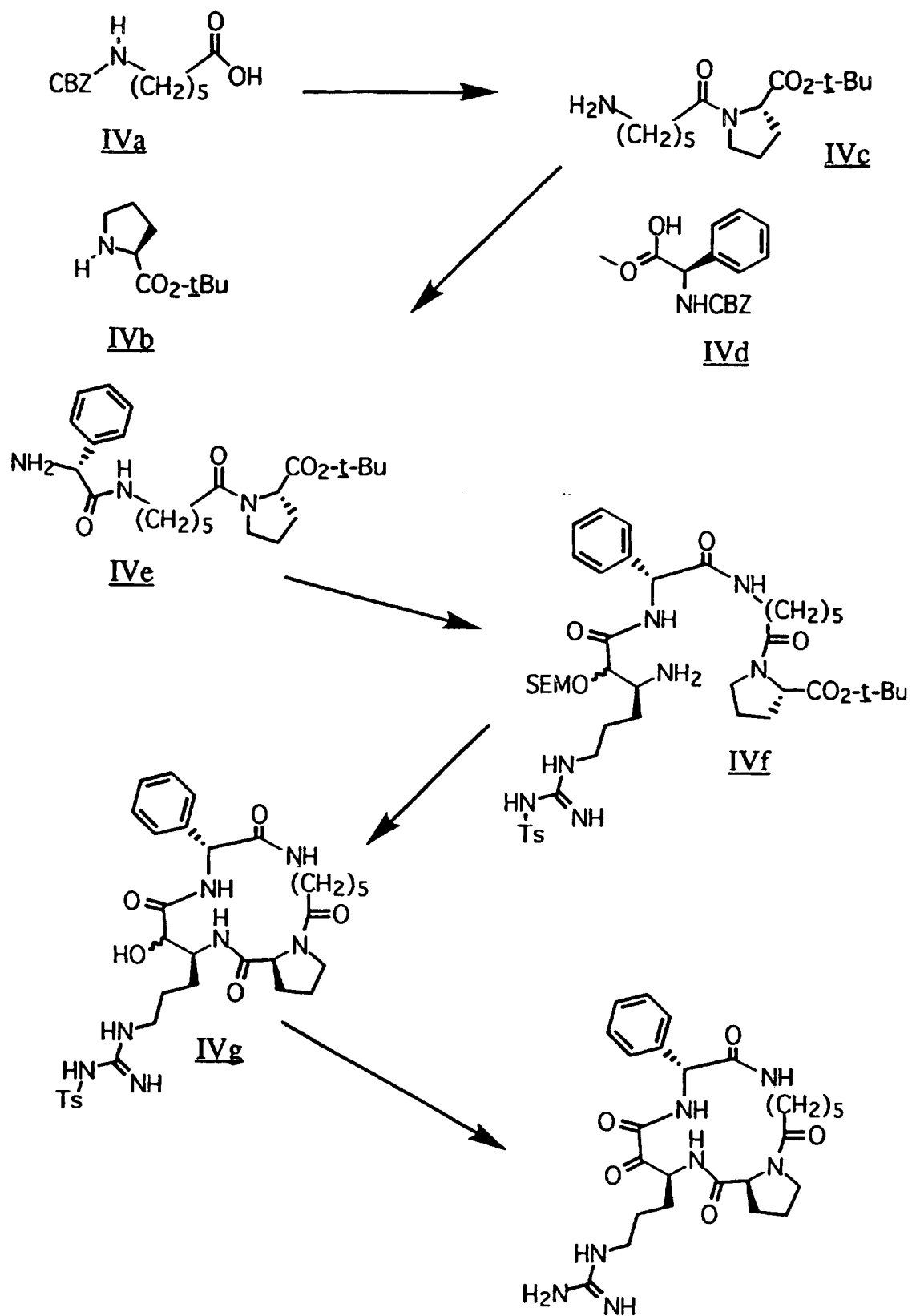


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and R₇ is butyl can be prepared by replacing IVd with D-norleucine. When active aromatic substituents are desired such as hydroxy, amino or carboxy, those compounds may be prepared as protected derivatives where the protecting groups well known in the art are described in Green, Theodora

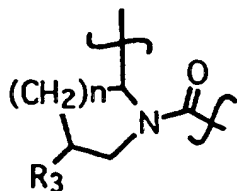
10 *Protecting Groups in Organic Synthesis*; John Wiley & Sons, New York, 1981. For example to prepare compound where R₇ is 4-hydroxybenzyl, a t-butyldimethylsilyl group is used as protecting group and removed with HF in the last step of the scheme.

SCHEME IV



Another method of synthesis is illustrated by Scheme V and may be used to prepare a compound of Formula I where m is 5;

A is



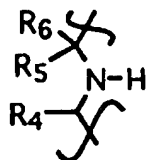
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where R₃ is methoxy;

n is 1;

B is

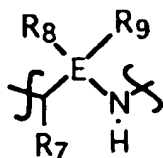
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where R₄ is 4-chlorobenzyl and R₅ is taken together with R₆ to form a carbonyl; and

15

G is



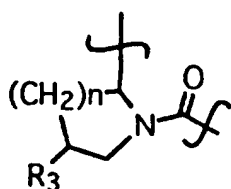
20 where E is carbon, R₈ and R₉ are hydrogen and R₇ is hydrogen.

A known Fmoc-protected amino aldehyde V_a, is reductively aminated at room temperature to a known t-butoxy-protected amino acid V_b, using NaB(O₂CCH₃)H in an inert solvent, such as CH₂Cl₂, over 5-24 h. The nitrogen of the resulting intermediate is protected with CBZ and the O- t-butoxy group is cleaved to give the acid V_c. This intermediate is coupled to a C-protected dipeptide V_d using HOBT/DCC followed by the removal of the Fmoc protection with an anhydrous base such as diethylamine to give V_e. Intermediate V_e is coupled to 6-[[imino[4-methylbenzenesulfonyl)-amino]methyl]amino]-2-(R,S)-[[2-(trimethylsilyl)ethoxy]methoxy]-3(S)-[9-fluorenylmethoxycarbonyl)-amino]hexanoic acid, (Maryanoff et al.

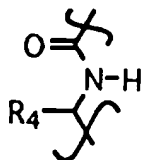
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Journal of the American Chemical Society 1995, 117, 1225-39) using HOBT/DCC at room temperature for 4-24 h in an inert solvent and deprotected with diethylamine to give the acyclic arginine derivative Yf. The t-butoxycarbonyl and SEM protecting groups are removed with TFA and the resulting intermediate is coupled at room temperature with BOP-Cl and DMAP in an inert solvent such as CH₂Cl₂ to give the hydroxy macrocyclic derivative Yg. Compound Yg is oxidized using periodinane in an anhydrous aprotic solvent and deprotected using HF in the presence of a carbocation scavenger to give a compound of Formula I.

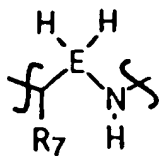
- 10 This Scheme V may be used to form the compounds of the invention where m is 2-12, A is



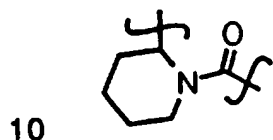
- 15 B is



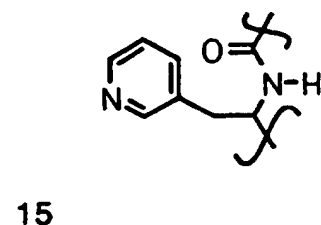
- where R₄ is hydrogen, C₁₋₅alkyl, phenyl, substituted phenyl (where the phenyl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine), phenylC₁₋₅alkyl, substituted phenylC₁₋₅alkyl (where the phenyl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine), 3-pyridylC₁₋₅alkyl, 4-pyridylC₁₋₅alkyl naphthyl or diphenylC₁₋₂alkyl, and G is



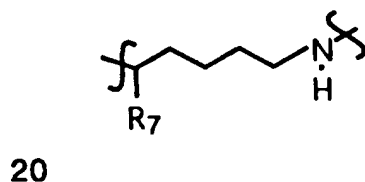
- where R₇ is hydrogen, C₁₋₅alkyl, phenyl, substituted phenyl (where the phenyl substituents are C₁₋₅alkoxy, fluorine or chlorine), phenylC₁₋₅alkyl, substituted phenylC₁₋₅alkyl (where the phenyl substituents are C₁₋₅alkoxy, fluorine or chlorine), 3-pyridylC₁₋₅alkyl, 4-pyridylC₁₋₅alkyl naphthyl or diphenylC₁₋₂alkyl and E is C(CH₂)_q, where q is 0-12. For example to prepare compounds where m is 2-12, the illustrated reactant Vb, is replaced with an analog of "m" methylenes such as 8-aminooctanoic acid -t-butyl ester. To prepare a compound where A is



and B is

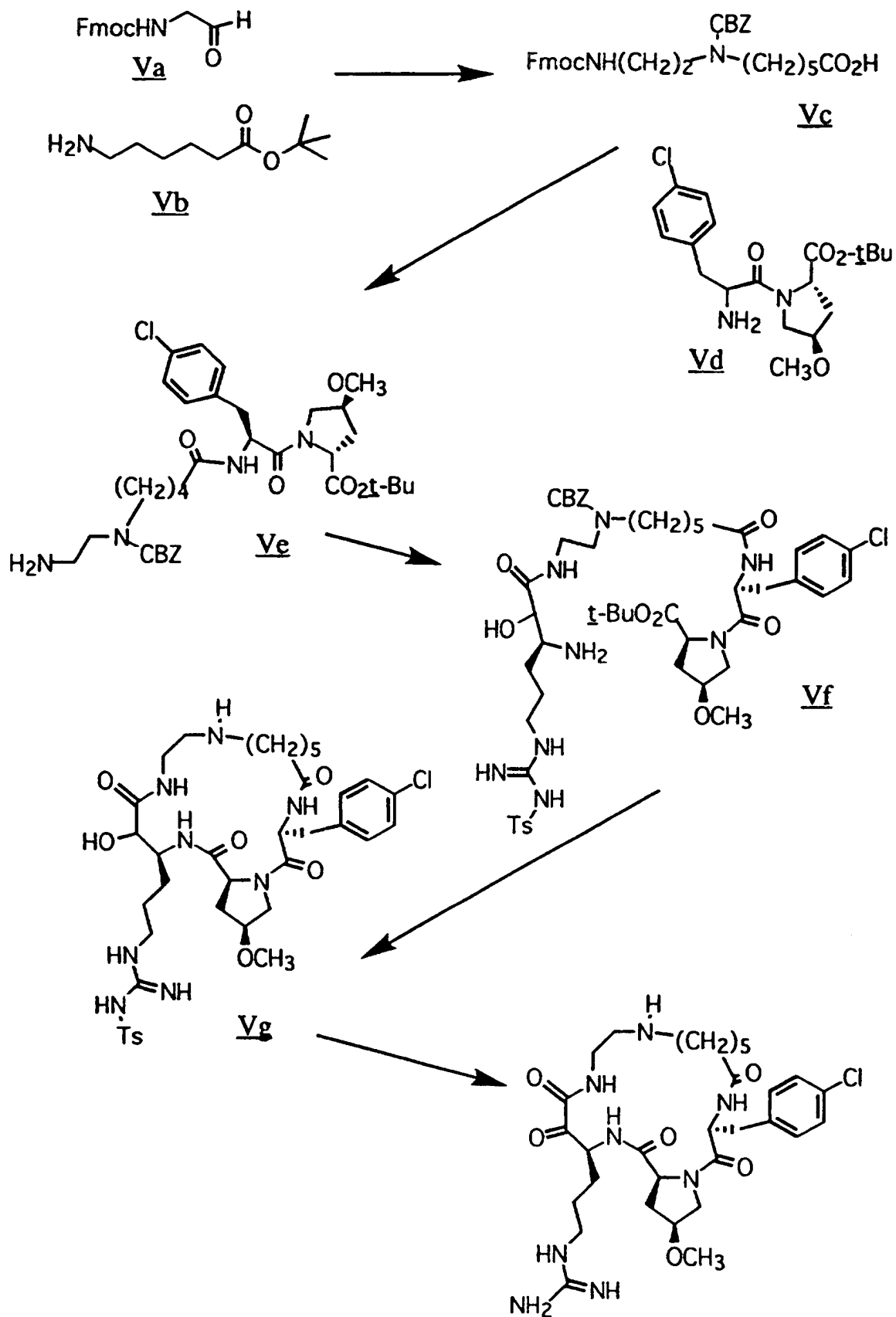


replace the illustrated reactant Vd with 3-pyridylalanine-D-pipecolinic acid -t-butyl ester. A compound where G is

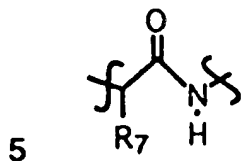


- and R₇ is hydrogen can be prepared by replacing Ya with 6-(N-9-fluorenylmethoxycarbonyl)aminobutylaldehyde. To prepare compounds where R₇ is other than hydrogen, start with an N-protected α-amino acid, reduce the carboxy to an aldehyde. Any of the standard reagents and conditions may be used including 1,1'-carbonyldiimidazole in THF at 0-10° C, followed by treatment with DIBAL/hexane at -42 °C. This α-substituted aldehyde is used in place of Ya and the remaining steps of the synthesis are carried through with only minor modifications.

SCHEME V



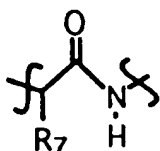
Yet another method of synthesis is illustrated by Scheme VI. This scheme is used to prepare a compound where m is 5 and G is



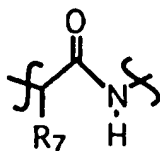
and R₇ is 4-chlorobenzyl.

A known N-protected amino acid VIa, is coupled at room temperature to a known C-protected amino acid VIb, using HOBT/DCC in an inert solvent, such as DMF, CH₃CN or THF, over 5-24 h to give VIc. Although HOBT/DCC is the preferred coupling agent other agents be used and include: BOP, BOP-Cl and PyBrOP. The preferred protecting groups are CBZ for nitrogen and t-butoxycarbonyl for carboxy; however, other protecting groups may be substituted as discussed previously. The protecting groups are removed by sequential treatment with TFA and Pd/(OH)₂/H₂ to give VIc. Intermediate VIc is coupled to 6-[[imino[4-methylbenzenesulfonyl]-amino]methyl]amino]-2-(R,S)-[[2-(trimethylsilyl)ethoxy]methoxy]-3(S)-[9-phenylmethoxycarbonyl]-amino]hexanoic acid, (Maryanoff *et al.* *Journal of the American Chemical Society* 1995, 117, 1225-39) using HOBT/DCC at room temperature for 4-24 h in an inert solvent to give VIId. The CBZ, t-butoxycarbonyl and SEM protecting groups are removed by sequential treatment with TFA and Pd(OH)₂/H₂ to give VIe. This intermediate is coupled at room temperature with BOP-Cl and DMAP in an inert solvent such as CH₂Cl₂ to give the hydroxy macrocyclic derivative VIIf. Compound VIIf is oxidized using periodinane in an anhydrous aprotic solvent and deprotected using HF in the presence of a carbocation scavenger such as anisole, thioanisole, pentamethylbenzene, dimethylsulfide or cresol to give a compound of Formula I.

This Scheme VI may be used to form the compounds of the invention where m is 2-12, and G is

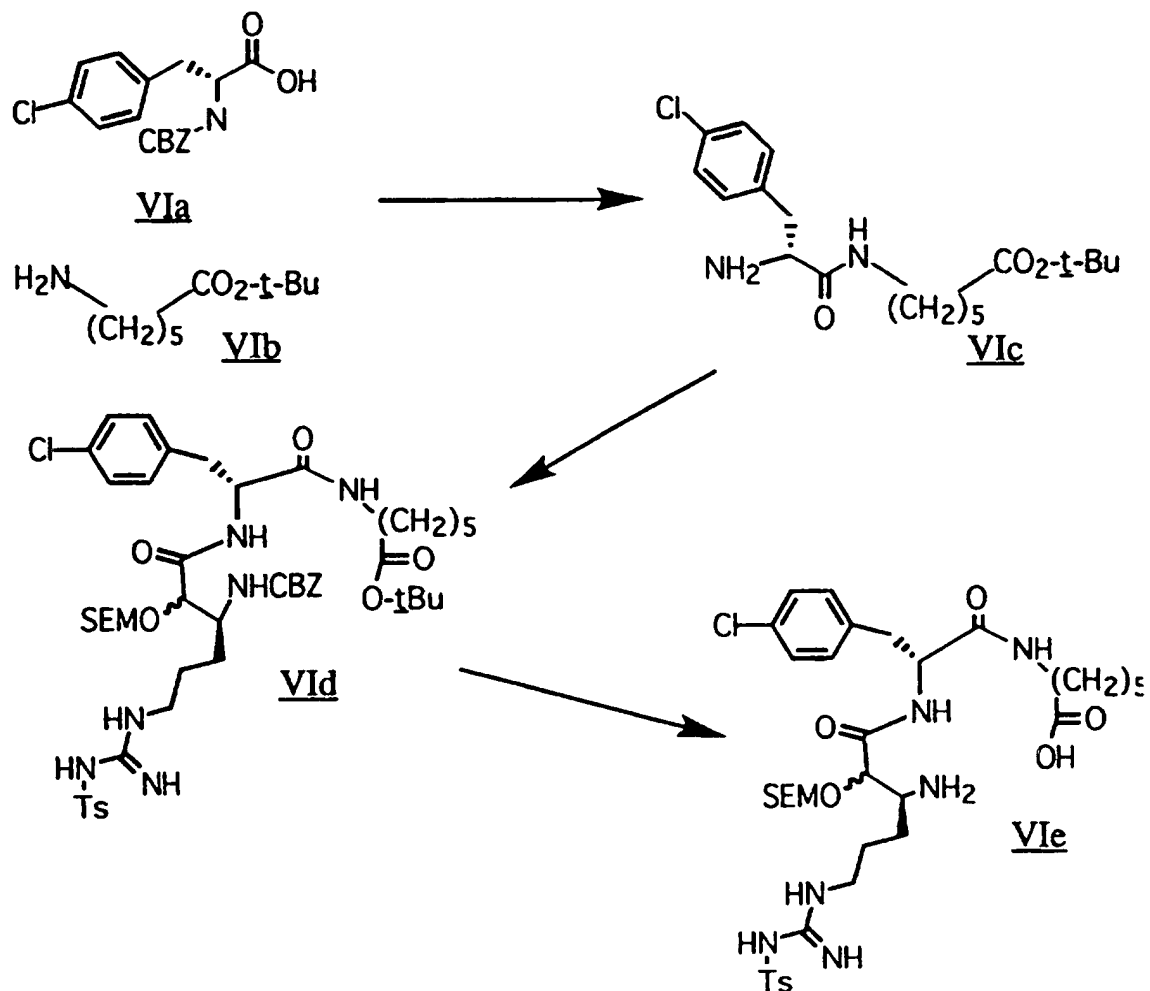


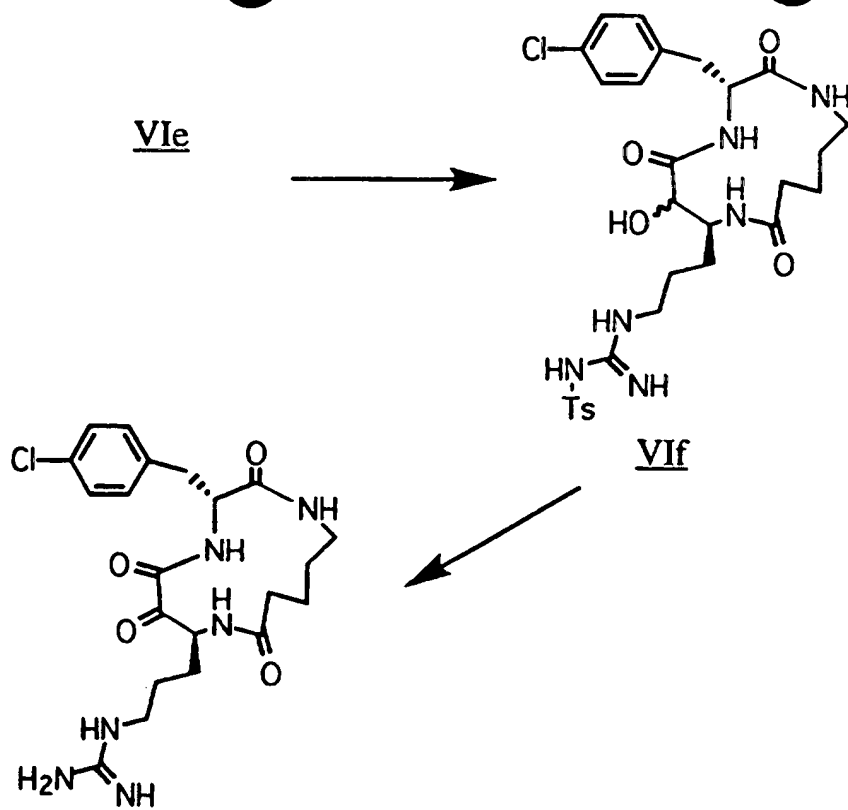
- where R₇ is hydrogen, C₁₋₅alkyl, phenyl, substituted phenyl (where the phenyl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine), phenylC₁₋₅alkyl, substituted phenylC₁₋₅alkyl (where the phenyl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine), 3-pyridylC₁₋₅alkyl, 4-pyridylC₁₋₅alkyl naphthyl or diphenylC₁₋₂alkyl. For example to prepare compounds where m is 2-12, the illustrated reactant VIb is replaced with an analog of "m" methylenes such as 8-aminooctanoic acid t-butyl ester. A compound where G is



- and R₇ is butyl can be prepared by replacing VIb with N-BOC-D-norleucine

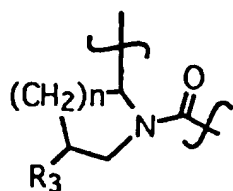
SCHEME VI





Scheme VII may be used to prepare the compounds of Formula III where m is 4, W is sulfur,

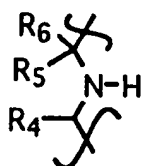
5 A is



where R_3 is hydrogen and n is 1;

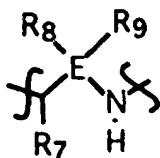
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B is



15 where R_4 is benzyl and R_5 is taken together with R_6 to form a carbonyl; and

G is



5

where E, R₈ and R₉ are taken together to form a carbonyl and R₇ is benzyl.

N- α -Fmoc-N- γ -tosyl-L-arginine is treated with carbonyldiimidazole at 0 °C in THF and reduced with DIBAL at about -48 °C to give the corresponding aldehyde. The cyanohydrin VIIb is produced by treating the aldehyde with KCN and H₂O at room temperature over several days in ethyl acetate. Treatment of VIIb with gaseous HCl in an alcohol such as MeOH at about -40 to -15 °C over several hours gives the imidate VIIc. Treatment of the imidate with VIIId (cysteine methyl ester hydrochloride) in an inert solvent such as CH₂Cl₂ at room temperature for 1-5 h gives the Fmoc protected amino alcohol VIIe. The hydroxy of VIIe can be converted to the trisilylalkyl ether with standard silylating agents such as *t* butyldimethylsilyltriflate and an organic base such as 2,6-lutidine at 0 °C. The Fmoc group is removed by treatment with an organic base such as diethyl amine at room temperature over 2-5 h. The free amine can be protected as the N-Boc derivative by treatment with di-*t*-butyl dicarbonate in an inert solvent at 0 °C over 16 h to give the 4,5-dihydrothiazole intermediate VIIIf. Intermediate VIIIf can be oxidized to the thiazole by treatment with an oxidizing agent such as MnO₂ in an inert solvent such as CH₂Cl₂ at room temperature over several hours. The isolated 5-carboalkoxy thiazole intermediate is saponified at room temperature with LiOH in dioxane/water to give the 5-carboxy thiazole derivative VIIg.

Derivative VIIg is coupled using HOBT/DCC to the C-protected tripeptide VIIh, where the peptide is prepared using any of the methods discussed in the previous schemes. Treatment with TFA removes the Boc group to give the coupled intermediate VIIi. This intermediate is treated at room temperature with BOP-Cl and DMAP in an inert solvent followed by removal of the silyl protecting group with Bu₄NF/THF at room temperature to give the macrocycle VIIj. This intermediate is oxidized using Dess-Martin periodinane in an anhydrous aprotic solvent and deprotected using HF in the presence of a carbocation scavenger to give a compound of Formula III.

To produce compounds where W is nitrogen or oxygen, VIId is replaced with 2,3-diamino propionic acid methyl ester or serine ethyl ester respectively.

Intermediate VIIc is used to produce all of the compounds of Formula III.

This intermediate can be used in place of 6-[[imino[4-methylbenzenesulfonyl)-

5 amino]methyl]amino]-2-(R,S)-[[2-(trimethylsilyl)ethoxy]methoxy]-3(S)-

[9-phenylmethoxycarbonyl)-amino]hexanoic acid or 6-[[imino[4-

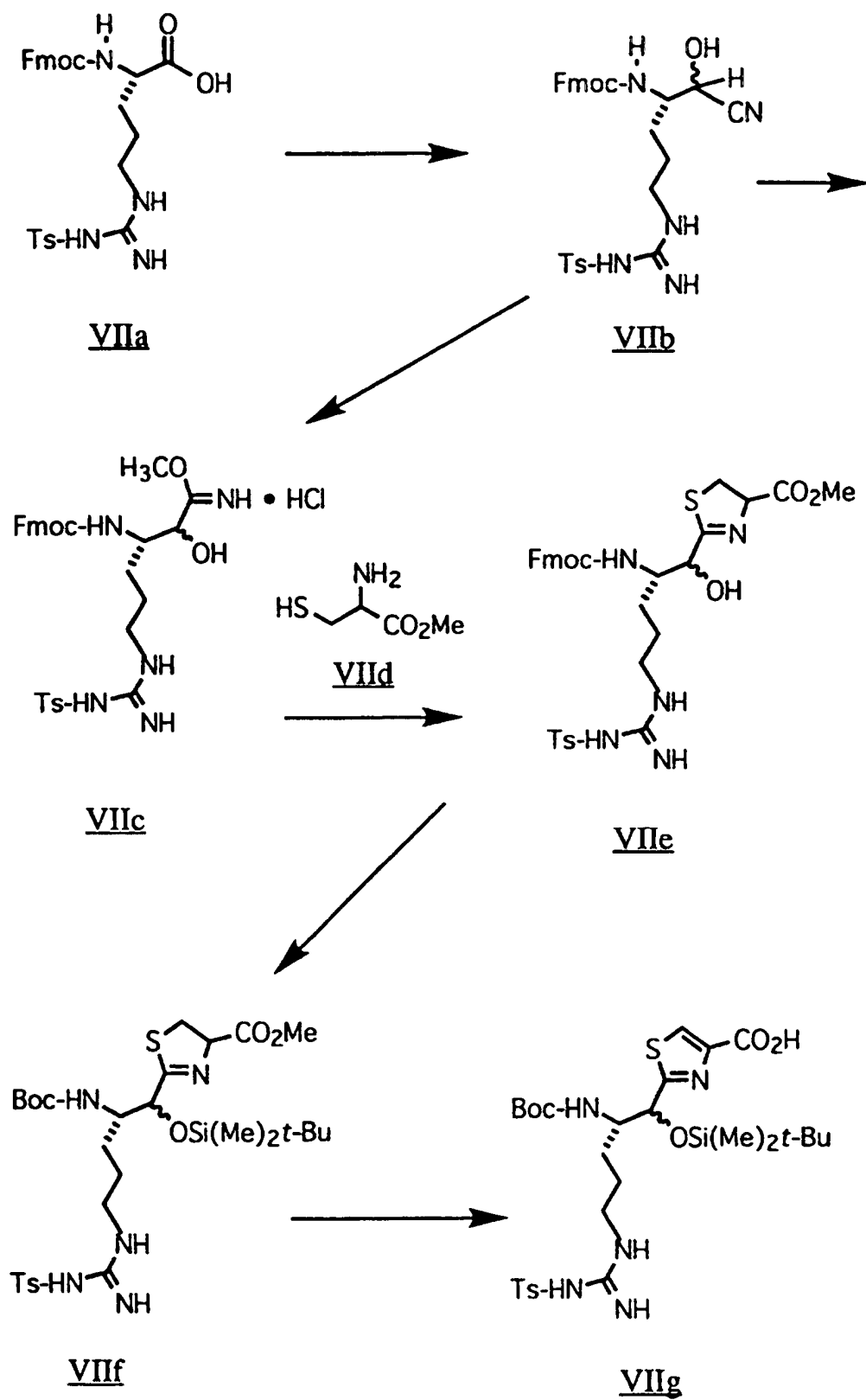
methylbenzenesulfonyl)-amino]methyl]amino]-2-(R,S)-[[2-

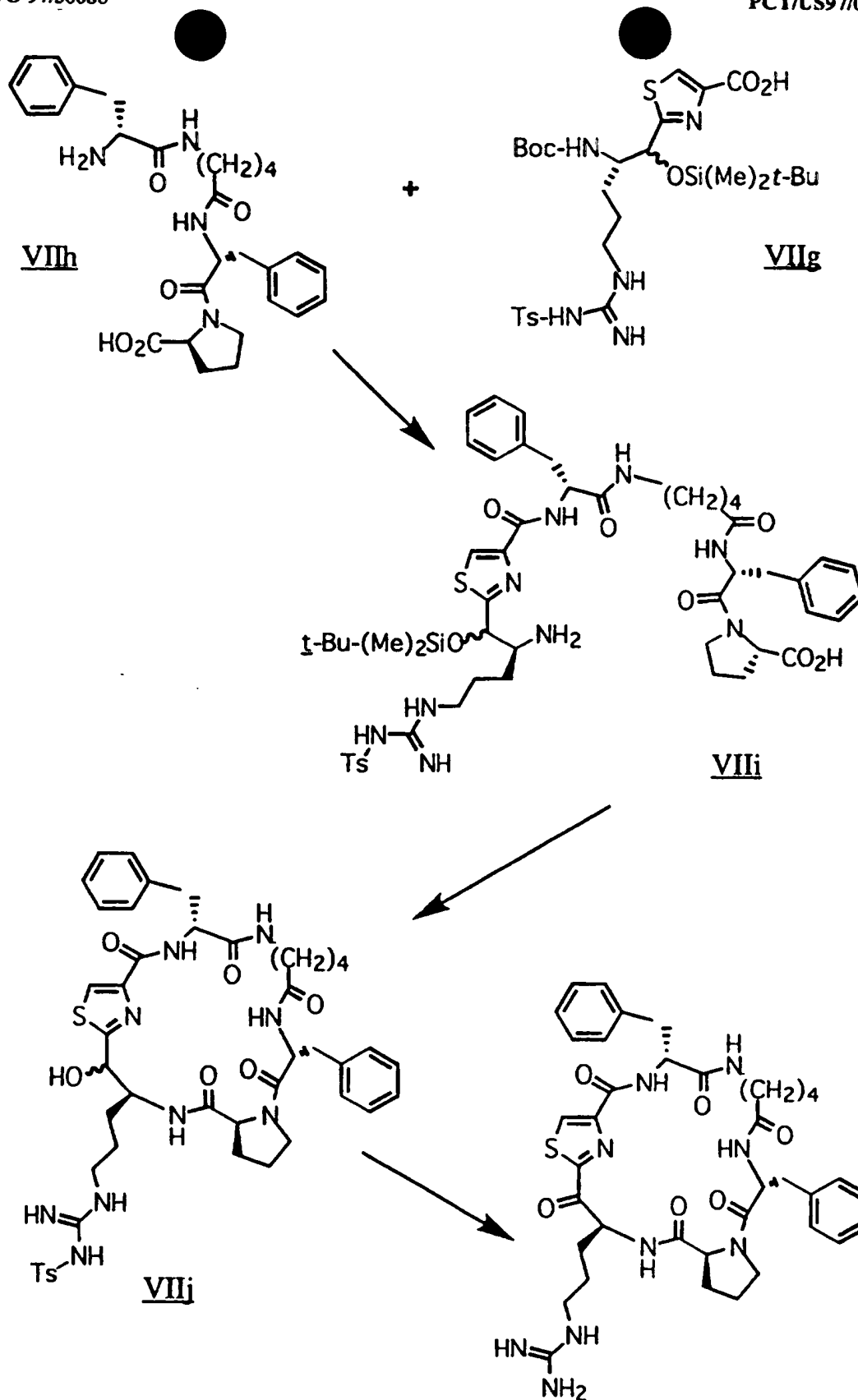
(trimethylsilyl)ethoxy]methoxy]-3(S)-[9-fluorenylmethoxycarbonyl)-

amino]hexanoic acid in Schemes I through VIII with only minor modification to

10 give the desired compounds.

SCHEME VII





The compounds of the invention were tested for their ability to inhibit thrombin mediated hydrolysis. Two in vitro enzyme assays were performed to give both Michaelis-Menten kinetics or slow, tight-binding kinetics. In addition, the compounds were tested in vitro for their ability to inhibit trypsin, as an indication of their selectivity

Thrombin-catalyzed hydrolysis rates were measured spectrophotometrically using commercial human alpha-thrombin (American Diagnostica), a chromogenic substrate (Spectrozyme® TH (H-D-HHT-Ala-Arg-pNA-2AcOH), American Diagnostica) in aqueous buffer (10 mM Tris, 10 mM Hepes, 150 mM NaCl, 0.1% PEG; pH 7.4), and a microplate reader (Molecular Devices). Changes in absorbance at 405 nm were monitored (Softmax, Molecular Devices), upon addition of enzyme, both with and without inhibitor present at 37°C over 30 minutes. Inhibition constants (K_i) were determined by fixing the enzyme and inhibitor concentrations and varying the substrate concentration (1 nM thrombin, 5-100 μ M Spectrozyme® TH). Michaelis-Menton kinetics were applied to the initial reaction slopes using the program K-Cat (Bio Metallics Inc.).

Trypsin-catalyzed hydrolysis rates were measured using the same method as the thrombin procedure. Bovine type 1 trypsin (Sigma) and Spectrozyme® TRY (Cbo-Gly-D-Ala-Arg-pNA•AcOH, American Diagnostics) replaced their thrombin equivalents in a concentration range of 3.2 U/ml trypsin and 0.1-0.3 mM Spectrozyme.

Compounds of the invention showed slow binding inhibition with thrombin which was demonstrated in the following assay. Serial dilutions of compounds and human alpha-thrombin (0.1 nM, American Diagnostica) were incubated at 25 °C for 4h. A chromogenic substrate was added (50 μ M Spectrozyme® TH (H-D-HHT-Ala-Arg-pNA•2AcOH), American Diagnostica) and the increase in absorbance at 405 nM was measured with a microplate reader (Molecular Devices) at 25 °C using an aqueous buffer (10 mM Tris, 10 mM Hepes, 150 mM NaCl, 0.1%PEG; pH 7.4). Data was collected over 4h and plotted (MOD v. Time). A compound was determined to be slow binding if the plot for any compound at any concentration was concave.

K_i -slow was determined by measuring enzyme-catalyzed hydrolysis rates. A mixture of human alpha-thrombin (0.1 nM, American Diagnostica), substrate (50 μ M Spectrozyme® TH (H-D-HHT-Ala-Arg-pNA•2AcOH), American Diagnostica), compound and aqueous buffer (10 mM Tris, 10 mM Hepes, 150 mM NaCl, 0.1%PEG; pH 7.4) was monitored over 4h for changes in absorbance at 405 nM at 25 °C. A vehicle mixture was run

under the same condition and inhibition constants were determined by applying the data to the following equation: $P = v_{st} - (1/k'(V_S - V_Z)(1 - \exp(-k't)))$. Plotting k' Vs. I gives K_i from the equation $k' = k_6(1 + S/K_m) + k_6/K_i(I)$. (Ref : Tight-Binding Inhibitors - I. Sungman Cha, Biochemical Pharmacology 1995. Vol 24 pp2177-2185). The K_i s and K_i -slow (μM) for representative compounds are listed in Table A. Cyclotheonamide, N-Me PPACK aldehyde ("GYKI-14766/LY-294468, Anticoagulant Thrombin Inhibitor", Drugs Future 1993, 18, 1159-1160) and argatroban ("Argatroban/Novastan/Slonnon, Anticoagulant Thrombin Inhibitor., Drugs Future 1990, 15, 1115-1116) were used as reference standards and their values are listed below. The compound numbers in the table correspond to the examples described hereinafter.

Table A

	Cpd. #	Thr K_i	Trp K_i	Thr K_i -slow
15	2	0.35±0.1 (N=8)	0.45±0.37 (N=6)	
	15	0.15±0.1 (N=10)	0.026±0.018 (N=8)	
	14	1.61±1.32 (N=10)	0.011±0.003 (N=5)	
	3	0.021±0.012 (N=6)	0.015±0.0038 (N=6)	
	11	0.0031±0.0008 (N=5)	0.004±0.0018 (N=6)	
20	18	3.8±0.2 (N=3)	0.31±0.01 (N=3)	
	16	85.9±16.3 (N=3)	0.62±0.48 (N=8)	
	7	0.2±0.072 (N=7)	0.039±0.025 (N=5)	
	6	0.021±0.005 (N=6)	0.0068±0.005 (N=8)	
	5	0.09±0.0086 (N=6)	0.085±0.029 (N=5)	
25	1	0.014±0.001 (N=5)	0.045±0.036 (N=6)	
	10	0.015±0.004 (N=6)	0.025±0.02 (N=4)	
	8	1.8±1 (N=6)	0.28±0.02 (N=6)	491.996±268.809 (N=)
	17	0.018±0.004 (N=6)	0.0029±0.0015 (N=5)	
	21	0.092±0.046 (N=5)	0.022±0.014 (N=6)	4.705±1.509 (N=2)
30	9	0.0099±0.0017 (N=7)	0.0021±0.0011 (N=5)	
	4	0.16±0.06 (N=9)	0.013±0.005 (N=6)	
	22	no activity at 50 μM		
	19	0.0053±0.0026 (N=6)	0.0025±0.00075 (N=5)	
	12	1±0.12 (N=6)	0.017±0.0073 (N=6)	
35	20	0.019±0.0044 (N=6)	0.0053±0.0026 (N=5)	1.362± 0.7 (N=3)
	23	1±0.4 (N=6)	0.066±0.026 (N=6)	
	13	0.0023±0.0005 (N=6)	0.0015±0.0009 (N=3)	
	CtA	.170 ± 0.08	23.0	4.0 ± 1.9 (N=4)

N-Me-PPAC	0.010	0.0039
Argatroban	0.010	2.9

As indicated by Table A, the compounds of Formula I may be used in pharmaceutical compositions to treat patients (humans and other primates) with thrombotic disorders in a similar manner as known heparins and coumarins. The compounds can be administered by any parenteral route (intravenous, intraperitoneal, subcutaneous, dermal patch), where the preferred route is intravenous infusion. Infusion doses can range from about 0.1-300 $\mu\text{g/kg/min}$ of inhibitor, admixed with a pharmaceutical carrier over a period ranging from several minutes to several days.

The pharmaceutical compositions can be prepared using conventional pharmaceutical excipients and compounding techniques. Oral dosage forms may be elixers, syrups, capsules tablets and the like. Where the typical solid carrier is an inert substance such as lactose, starch, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, mannitol and the like; and typical liquid oral excipients include ethanol, glycerol, water and the like. All excipients may be mixed as needed with disintegrants, diluents, granulating agents, lubricants, binders and the like using conventional techniques known to those skilled in the art of preparing dosage forms. Parenteral dosage forms may be prepared using water or another sterile carrier.

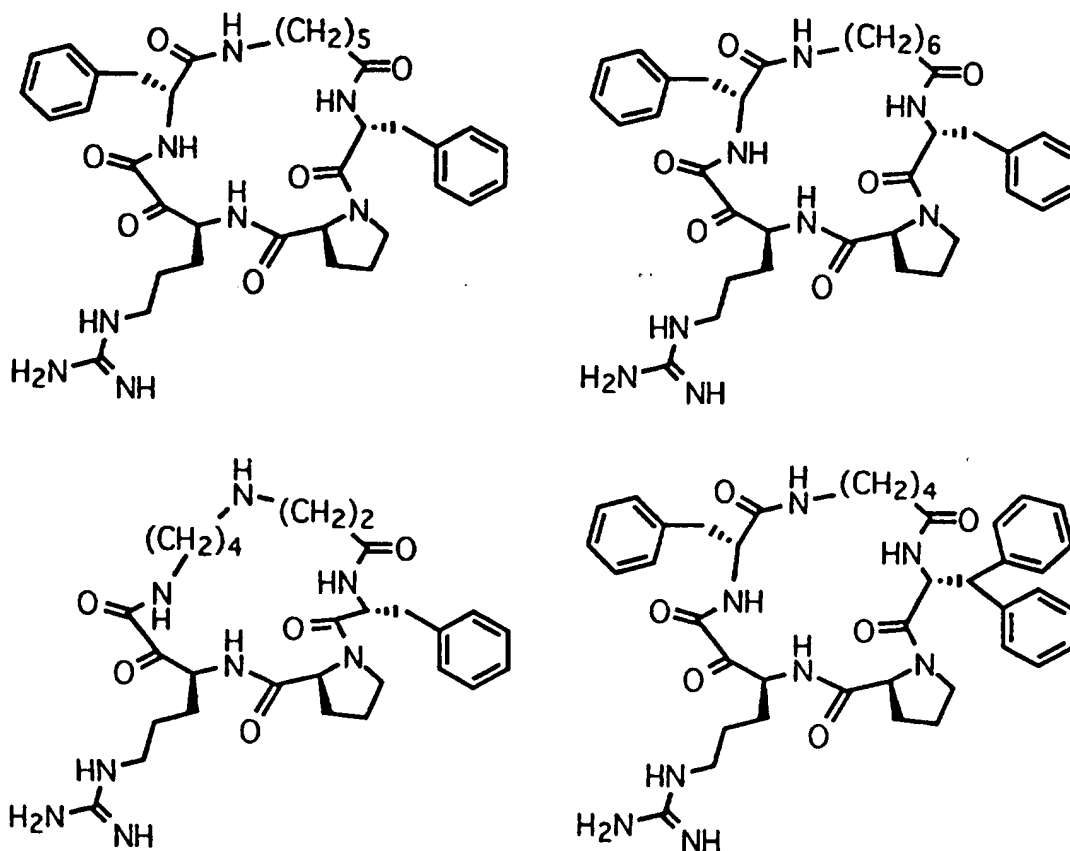
Typically the compounds of Formula I are isolated and used as their pharmaceutically acceptable salts. Examples of such salts include hydrobromic, hydroiodic, hydrochloric, perchloric, sulfuric, maleic, fumaric, malic, tartatic, citric, benzoic, mandelic, methanesulfonic, hydroethanesulfonic, benzenesulfonic, oxalic, pamoic, 2-naphthalenesulfonic, *p*-toluenesulfonic, cyclohexanesulfamic and saccharic.

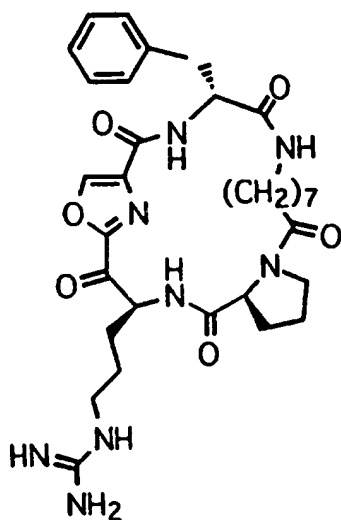
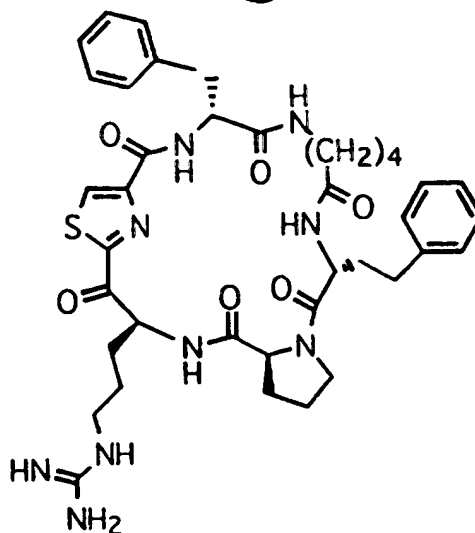
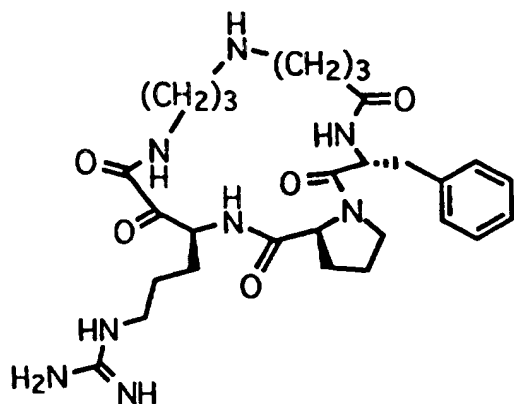
In addition to the treatment of thrombotic disorders, the compounds of Formula I may be used to prevent coagulation of stored blood samples and as coatings on medical devices such as stents and orthopedic devices. Generally they may be used in any circumstance where one seeks to inhibit coagulation by placing the compounds in contact with the medium containing thrombin. Those experienced in the use of anticoagulant agents, may find a variety of other uses for the thrombin inhibitors of this invention. These uses are considered to be within the scope of this invention, for this invention contemplates the use of compounds of Formula I as antithrombotic agents.

Yet another use for the compounds of the invention is as trypsin inhibitors. Inhibitors of trypsin have been used clinically in the treatment of pancreatic disorders, such as pancreatitis. The IC_{50} values for the compounds of the invention compare favorably with the pancreatic agents camostat mesilate and nafamostat (IC_{50} s, 1×10^{-8} and 1.3×10^{-8} respectively). The compounds of Formula I may be used in the same manner as those therapeutic agents.

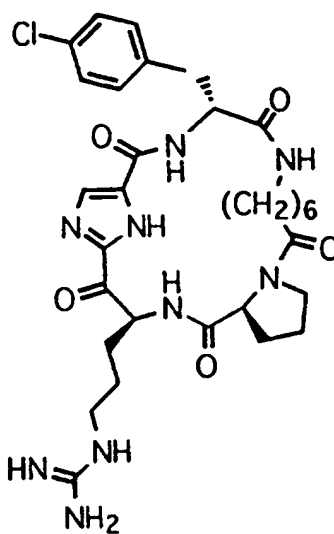
Although all of the claimed compounds are useful as thrombin or trypsin inhibitors, the preferred compounds of Formula I include

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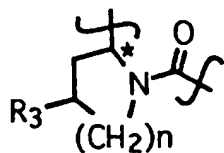




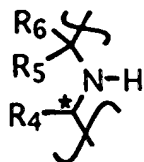
and



- 5 With respect to compounds of Formulas I and II, the particularly preferred substituents are as follows. The particularly preferred "A"s are



- 10 where n is 1, R₃ is hydrogen and the preferred stereochemistry of the starred carbon is S.
The particularly preferred "B"s are

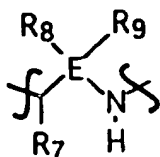


where R₅ and R₆ are taken with the carbon to which they are each attached to form a carbonyl; and R₄ is naphthylmethyl, diphenylmethyl,

- 5 phenylC₁₋₅alkyl or substituted phenylC₁₋₅alkyl where the phenyl substituents are chlorine or fluorine. The preferred stereochemistry of the starred (*) carbon is R.

10

The particularly preferred "G"s are



15

where R₈ and R₉ are taken with the carbon to which each is attached to form a carbonyl; and R₇ is naphthylmethyl, diphenylmethyl, phenylC₁₋₅alkyl or substituted phenylC₁₋₅alkyl where the phenyl substituents are chlorine or fluorine. The ring size of the macrocycle is determined by A, B, G and m, where

- 20 a ring size of 15 to 25 is particularly preferred.

With respect to the compounds of Formula III, the particularly preferred "W" is sulfur. All other particularly preferred substituents are as described for Formulas I and II.

In order to illustrate the invention the following examples are included.

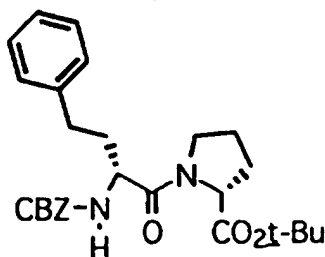
- 25 These examples do not limit the invention. They are only meant to suggest a method of practicing the invention. Those skilled in the art may find other methods of practicing the invention, which are obvious to them. However, those methods are deemed to be within the scope of this invention.

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EXAMPLE 1

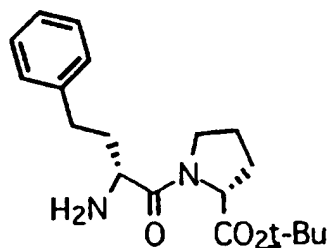
5R, 18S, 21S-N-[3-(4, 7, 16, 17, 20-PENTAOXO-5-PHENETHYLEICOSAHYDRO-3a, 6, 15, 19 - TETRAAZACYCLOPENTACYCLONONADECENE-18-YL) PROPYL] GUANIDINE

Step 1a

**1a**

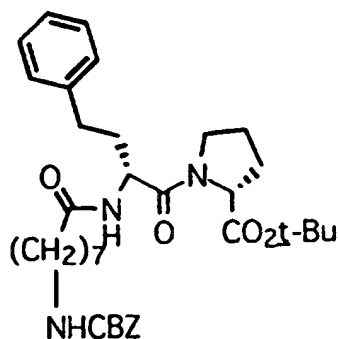
A solution of CBZ-D-homophenylalanine 5.6 g (18 mmol), ProO-*t*-Bu (3.4 g, 19.8 mmol) and HOBT, (3.65 g, 27 mmol) in CH₃CN (70 mL) was stirred for 20 min, treated with a solution of DCC (4 g, 19.8 mmol) in CH₃CN (30 mL) and stirred overnight. This mixture was filtered, the filtrate was concentrated and dissolved in CHCl₃ (400 mL). This solution was washed with successive portions of 2% Na₂CO₃(aq) (100 mL) and brine (100 mL). The resulting organic layer was dried (Na₂SO₄), concentrated in vacuo and purified by flash column chromatography (silica, CHCl₃) to afford **1a** as an oil: (8.4g).

Step 1b

**1b**

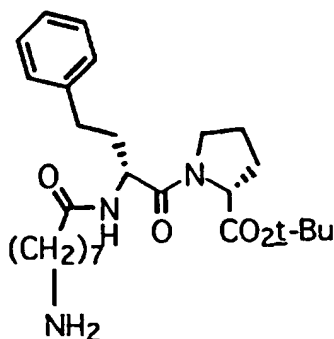
A mixture **1a** (5.0 g) and Pd(OH)₂-C in MeOH (100 mL) was shaken under 20 psig for 1.5 h. The catalyst was filtered, and the filtrate concentrated to give the free amine **1b**, as an oil (61.6 g).

Step 1c

**1c**

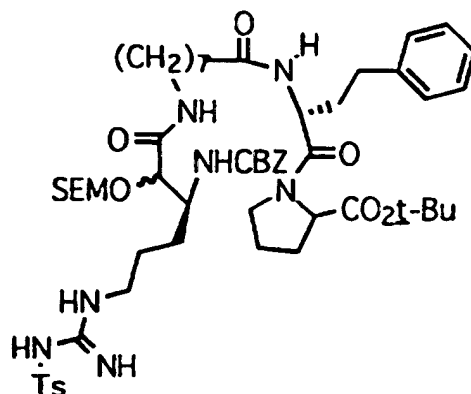
A solution of DCC (3.8 g, 18.5 mmol) in CH₃CN (40 mL) was added to a stirred mixture of **1b** (6.2 g, 18.5 mmol) 8-carbobenzoxyminoctanoic acid (4.94 g, 16.8 mmol) and HOBT (3.4 g, 25.2 mmol) in CH₃CN (300 mL). The resulting mixture was stirred for 16 h, filtered and concentrated *in vacuo*. The residue was dissolved in CHCl₃, washed sequentially with 5% Na₂CO₃(aq) and brine, dried (Na₂SO₄), and concentrated *in vacuo*. The residue was purified by flash column chromatography (ether-MeOH; 100%→95:5) to give ester **1c** as an oil: (7.8 g, 70%); m/e = 607 (MH⁺).

Step 1d

**1d**

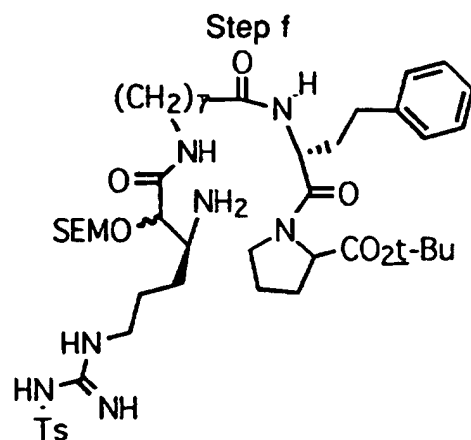
A mixture of **1c**, (7.8 g, 12.8 mmol), 20% Pd(OH)₂/C (5.0 g) and 150 mL of MeOH was shaken under 20 psig of H₂ for 3 h. The mixture was filtered and concentrated to give the amine **1d** as an oil: (5.5 g, 91%), m/e = 474 (MH⁺).

Step 1e

**1e**

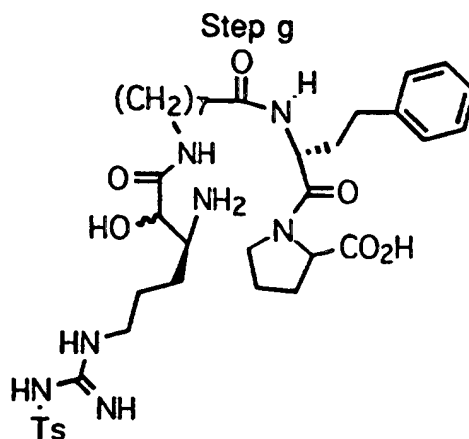
A solution of DCC (0.91, 4.4 mmol) in DMF (15 mL) was added to a solution of 6-[[[imino[4-methylbenzenesulfonyl]amino]methyl]amino]-2-(R,S)-[[2-(trimethylsilyl)ethoxy]methoxy]-3(S)-[9-phenylmethoxycarbonyl]-amino]hexanoic acid, (2.5 g, 4.0 mmol: Maryanoff *et al.* *Journal of the American Chemical Society* 1995, 117, 1225-39), amine **1d** (2.0 g, 4.4 mmol) and HOBT (0.8 g) in DMF (150 mL). This mixture was stirred overnight, and filtered. The filter cake was washed with CH₃CN, and the filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, 100% CHCl₃, then 2% MeOH-CHCl₃) to give ester **1e** as a foam: (3.4 g 78%); m/e = 1078 (MH⁺).

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**1f**

20

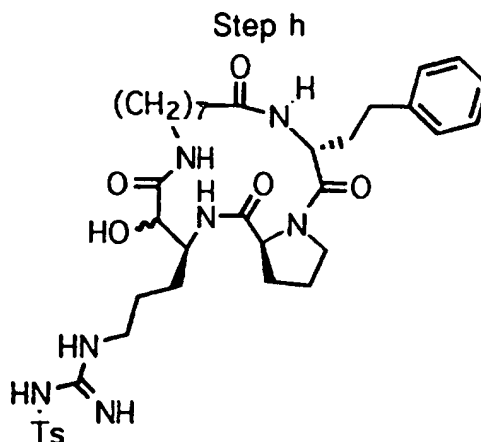
A solution of **1e** (3.3 g) in MeOH (50 mL) was treated with 20% Pd(OH)₂/C (2.0 g) and shaken under 20 psig of H₂ for 3 h. The mixture was filtered and concentrated to the ester **1f** as a foam: (2.7 g); m/e = 944 (MH⁺).



- 5 A solution **1f** (2.6 g) in CH₂Cl₂ (10 mL) was added to a solution of 1:1 CH₂Cl₂:trifluoroacetic acid (40 mL) at 0 °C and stirred for 2.5 h. Volatiles were removed under a stream of N₂, and the resulting gum was triturated three times with ether to give the acid **1g** as a white solid: (2.5 g); m/e = 758 (MH⁺).

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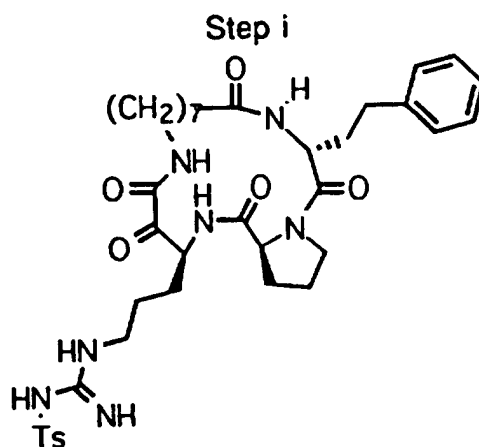
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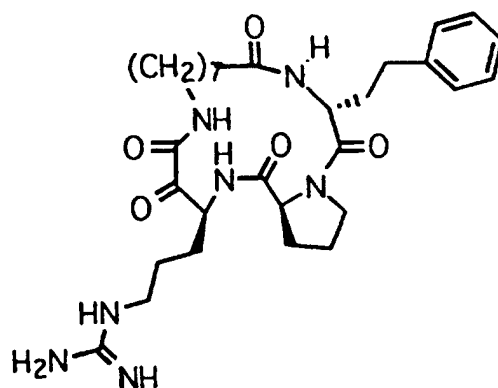
- A mixture of **1g** (1.2 g, 1.38 mmol) in 1.4 L of CH₂Cl₂ was treated with DMAP (0.93 g, 7.6 mmol), and stirred for 20 min. BOP-Cl (0.1, 2.76 mmol) was

added and the mixture was stirred for another 2 h and concentrated in vacuo. The residue was dissolved in CH₂Cl₂ (500 mL) and washed twice with 10% citric acid (aq)(2x250 mL). The organic layer was washed with brine, dried (Na₂SO₄), filtered, and concentrated in vacuo. The residue was purified by
 5 flash column chromatography (CHCl₃-MeOH; 100% -> 90%; silica gel) to give the coupled intermediate 1h: (600 mg, 81 %); m/e = 740 (MH⁺).



10

Dess-Martin periodinane (499 mg, 1.2 mmol) was added to a stirred solution of 1h (580 mg, 0.78 mmol) in CH₂Cl₂ (50 mL) at room temperature. This mixture was stirred for 1.5 h, treated with an excess of 25% Na₂S₂O₄ (aq) in NaHCO₃ (sat'd. aq) and stirred for another 5 min. The aqueous layer was
 15 extracted with several portions of CH₂Cl₂ and the combined organic extracts were washed twice with NaCl (sat'd. aq), dried (Na₂SO₄), filtered and concentrated to give the diketone 1i as a white solid: (495 mg); m/e = 738 (MH⁺).



20

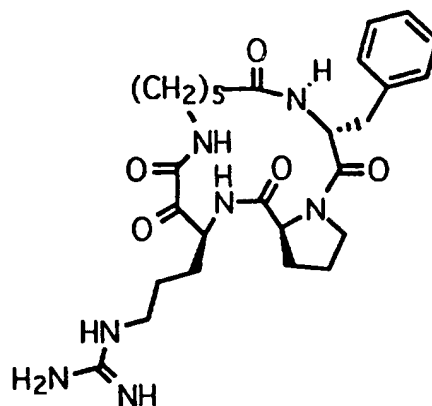
5R, 18S, 21S-N-[3-(4, 7, 16, 17, 20-PENTAOXO-5-PHENETHYLEICOSAHYDRO-3a, 6, 15, 19 -TETRAAZACYCLOPENTACYCLONONADECENE-18-YL)

PROPYL] GUANIDINE
COMPOUND 1

A suspension of **1i** (480 mg, 0.65 mmol) in anisole (3 mL) was cooled to -78°C and treated with anhydrous HF (ca. 10 mL) using a standard HF apparatus. This mixture was stirred at 0°C for 3.5 h, concentrated in vacuo and triturated twice with 25 mL portions of ether. A solid was collected, washed with ether, and purified by reverse-phase HPLC (MeCN-water-TFA, 35:65:0.2). The resulting solid was lyophilized to give the title compound as a white solid: 272 mg; mp 50 °C; FAB-MS m/e 584 (MH⁺);

Anal Calcd. for C₃₀H₄₅N₇O₅ • 2.5 CF₃CO₂H • 1.25 H₂O:
Calcd.: C, 47.16; H, 5.65; N, 11.00; H₂O, 2.53.
Found: C, 46.90; H, 5.23; N, 11.12; H₂O 2.60.

EXAMPLE 2



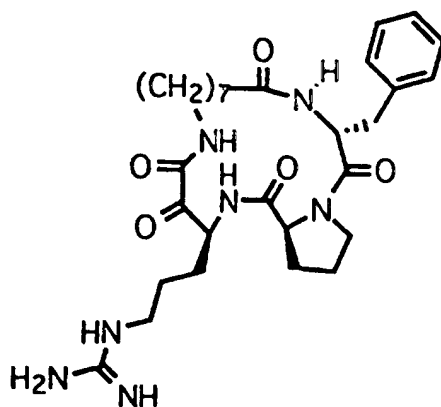
5R, 16S, 19S-N-[3-(5-BENZYL-4, 7, 14, 15, 18-PENTAOXOOCTADECYCL-3a, 6, 13, 17-(TETRAAZACYCLOPENTACYCLOHEPTADECEN-16-YL)PROPYL]-GUANIDINE DI-TRIFLUOROACETIC ACID SESQUIHYDRATE.

COMPOUND 2

Compound 2 was prepared using the general method of Example 1. CBZ-D-PheOH replaced CBZ-D-homophenylalanine in Step 1a and 5-carbobenzoxycarboxypentanoic acid replaced 8-carbobenzoxycarboxyoctanoic acid in Step 1c to give the title compound as a solid. FAB-MS m/e 541 (MH⁺);

Anal. Calc'd for C₂₇H₃₉N₇O₅•2(C₂HF₃O₂)•1.5 H₂O:
Calc'd: C, 46.73; H, 5.57; N, 12.31, H₂O, 3.39.
Found: C, 46.71; H, 5.73; N, 12.78; H₂O, 3.52.

EXAMPLE 3



2S, 5S, 18R-N-[3-(18-BENZYL)-3,6,7,16,19-
(PENTAOXOEICOSAHYDRO)-1A, 4, 8, 17-
5 (TETRAAZACYCLOPENTACYCLONONODECEN-5-YL)PROPYL]
GUANIDINE TRIFLUOROACETIC ACID HYDRATE.

COMPOUND 3

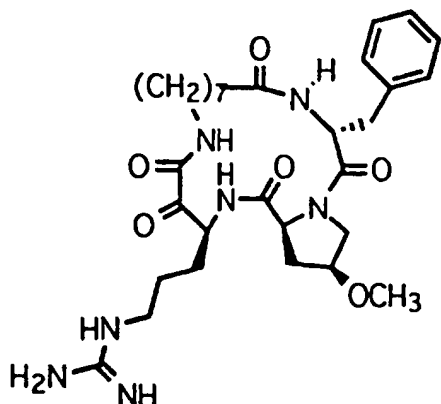
Compound 3 was prepared following the method of Example 1 with only
slight modifications. CBZ-D-PheOH replaced CBZ-D-homophenylalanine in
10 Step 1a to give the title compound as a solid. FAB-MS m/z 570, (MH⁺)

Anal. Calc'd for C₂₉H₄₃N₇O₅•2.5C₂HF₃O₂•H₂O;

Calc'd: C, 46.79; H, 5.49; N, 11.23; H₂O, 2.06.

Found: C, 47.05; H, 5.43; N, 11.29; H₂O, 2.25.

EXAMPLE 4



2S, 5R, 18S, 21S-[3-(5-BENZYL-2METHOXY-4, 7, 16, 17, 20-
PENTAOXOEICOSAHYDRO-3a, 6, 15, 19-
TETRAAZACYCLOPENTACYCLONONADECEN-18-YL)
20 PROPPYL] GUANIDINE TRIFLUOROACETIC ACID HYDRATE

COMPOUND 4

Compound 4 was prepared following the method of Example 1 with only slight modifications. CBZ-D-PheOH replaced CBZ-D-homophenylalanine in Step 1a and *cis*-methoxyproline (prepared according to Barlos, K., et al. *Tetrahedron Lett.* 1983, 39, 475) replaced ProO-*t*-Bu in the same step to give the title

5 compound as a solid: FAB-MS m/z 600 (MH^+);

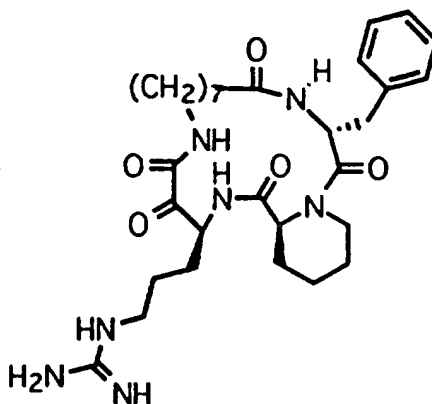
Anal. Calc'd for $C_{30}H_{45}N_7O_6 \cdot 2.25 C_2HF_3O_2 \cdot 1.5 H_2O$

Calc'd: C, 46.91; H, 5.73; N, 11.10; H_2O , 3.05

Found: C, 46.90; H, 6.03; N, 11.44; H_2O , 3.00.

10

EXAMPLE 5



6R, 19S, 22S-N-[3-(6-BENZYL-5, 8, 17, 18, 21-
PENTAOXODOCOSAHYDRO-4a, 7, 16, 20-
TETRAAZABENCBZOCYCLONONADecen-19-yl) PROPYL]
15 GUANIDINE TRIFLUOROACETIC ACID HYDRATE

COMPOUND 5

Compound 5 was prepared following the method of Example 1 with only slight modifications. CBZ-D-PheOH replaced CBZ-D-homophenylalanine in Step 1a and L-pipecolic acid replaced ProO-*t*-Bu in the same step to give the

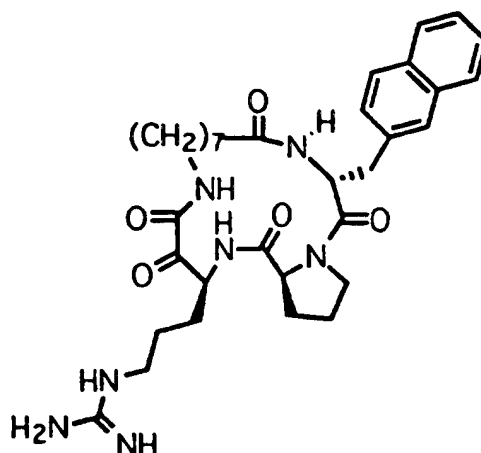
20 title compound as a solid: FAB-MS m/z 584 (MH^+); Anal. Calc'd for

$C_{30}H_{45}N_7O_5 \cdot 2.0 C_2HF_3O_2 \cdot 1.0 H_2O$:

Calc'd: C, 49.21; H, 5.95; N, 11.82; H_2O , 2.17

Found: C, 49.28; H, 5.66; N, 11.67, H_2O , 2.56.

EXAMPLE 6



5R, 2S, 18S-N-[3-(5-NAPHTHALEN-2-YLMETHYL-4, 17, 16, 17, 20-
 PENTAOXOEICOSAHYDRO-3a, 6, 15, 19-
 5 TETRAAZACYCLOPENTACYCLONONADECEN-18-YL)PROPYL]
 GUANIDINE TRIFLUOROACETATE HYDRATE
 COMPOUND 6

Compound 6 was prepared following the method of Example 1 with only slight modifications. CBZ-D-2-naphthylalanine replaced

10 CBZ-D-homophenylalanine in Step 1a to give the title compound as a solid:

FAB-MS m/z: FAB-MS m/z 620 (MH⁺); Anal. Calc'd for C₃₃H₄₅N₇O₅•1.5

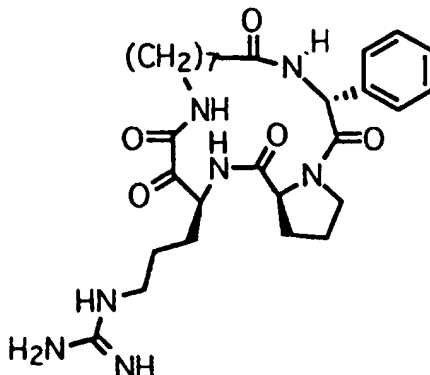
C₂HF₃O₂•1.75 H₂O:

Calcd: C, 51.80; H, 5.93; N, 11.59; H₂O, 3.19

Found: C, 51.44; H, 5.95; N, 11.44; H₂O, 3.23.

15

EXAMPLE 7

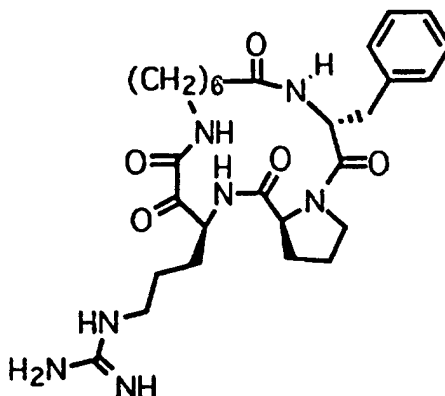


3S, 16R, 19S-N-[3-(1, 4, 5, 14, 17-PENTAOXO-16-PHENYL-2, 6,
 15, 18-TETRAAZACYCLOPENTACYCLONONADECAN-3-
 20 YL)PROPYL] GUANIDINE TRIFLUOROACETIC ACID HYDRATE
 COMPOUND 7

Compound 7 was prepared following the method of Example 1 with only slight modifications. CBZ-D-phenylglycine replaced CBZ-D-homophenylalanine in Step 1a to give the title compound as a solid: FAB-MS m/z 556 (MH^+); Anal. Calcd for $C_{28}H_{41}N_7O_5 \cdot 1.75 C_2HF_3O_2 \cdot 1.5 H_2O$:

- 5 Calc'd: C, 48.37; H, 5.90; N, 12.53; H₂O 3.45
 Found: C, 48.40; H, 5.95; N, 12.52; H₂O, 3.64.

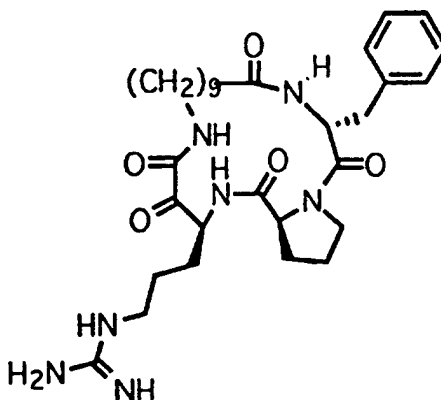
EXAMPLE 8



- 10 5R, 17S, 19AS-N-[3-(5-BENZYL-4, 7, 15, 16, 19-
 PENTAOXOOCTADECYDRO-3a, 6, 14, 18-
 TETRAAZACYCLOPENTACYCLOOCTADecen-17-yl)propyl]
 GUANIDINE TRIFLUOROACETIC ACID HYDRATE
 COMPOUND 8

- 15 Compound 8 was prepared using the general method of Example 1.
 CBZ-D-PheOH replaced CBZ-D-homophenylalanine in Step 1a and 7-
 carbobenzyloxyaminoheptanoic acid replaced 8-carbobenzyloxyaminooctanoic
 acid in Step 1c to give the title compound as a solid: FAB-MS m/z 556 (MH^+);
 Anal. Calc'd for $C_{28}H_{41}N_7O_5 \cdot 1.5 C_2HF_3O_2 \cdot 2.0 H_2O$:
 20 Calc'd: C, 48.82; H, 6.15; N, 12.85, H₂O, 4.72
 Found: C, 48.68; H, 6.07; N, 12.74, H₂O, 4.83.

EXAMPLE 9



5R, 20S, 23S-[3-(5-BENZYL-4, 7, 18, 19, 22-PENTAOXOCYCLOEICOSAHYDRO-3A, 6, 17, 21-TETRAAZACYCLOPENTACYCLOHENEICOSEN-20-YL)PROPYL]GUANIDINE TRIFLUOROACETIC ACID HYDRATE
COMPOUND 9

5

A slurry of 9-cyanopelargonic acid (8.6 g, 48 mmol), a catalytic amount 5%Rh/Al₂O₃, and 200 mL of 2.0 N NH₃-EtOH was shaken under 50 psig of H₂ pressure for 6 h, then filtered through dicalite. The filter pad was washed with 100 mL of hot 1:1 MeOH-H₂O, and the combined filtrates were concentrated to give 6.1 g of 10-aminodecanoic acid. The crude product (5.7 g) was dissolved in 15.5 mL of 2N NaOH and treated simultaneously with 23 mL of 2N NaOH and 5.8 g of carbobenzoxychloride at 0 °C with vigorous stirring over 0.5 h. Water and 2N NaOH were added as needed to maintain stirring and a pH between 10-14. After stirring for 2.5 h, the reaction was diluted with 400 mL of H₂O and filtered through dicalite. The filtrate was acidified (pH 2) with H₂SO₄, then extracted with ether. The combined ether extracts were dried (Na₂SO₄), filtered and concentrated. The residue was dissolved in CH₃CN, filtered, and the filtrate concentrated to afford 5.3 g of 10-(*N*-carbobenzoxy)-aminodecanoic acid which was used without further purification: FAB-MS m/z 322 (MH⁺).

20

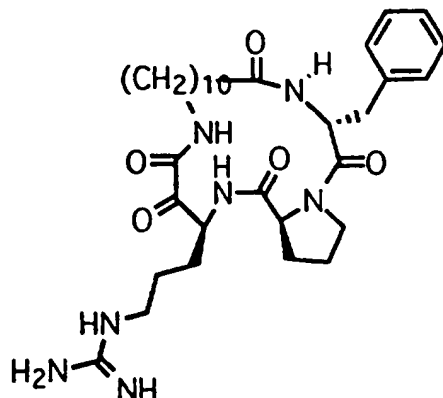
Compound 9 was prepared using the general method of Example 1. CBZ-D-PheOH replaced CBZ-D-homophenylalanine in Step 1a and 10-(*N*-carbobenzoxy)-aminodecanoic acid replaced 8-carbobenzoxycarboxyaminooctanoic acid in Step 1c to give the title compound as a solid: FAB-MS m/z 598 (MH⁺); Anal Calc'd for C₃₁H₄₇N₇O₅·1.75 C₂HF₃O₂·1.75 H₂O;

25

Calc'd: C, 50.00; H, 6.35; N, 11.83; H₂O, 3.80

Found: C, 49.62; H, 6.23; N, 11.93; H₂O, 3.46.

EXAMPLE 10



21S, 24S, 27R-N-[3-(5-BENCBZYL-4, 7, 19, 20, 23-
PENTAOXOTETRACOSAHYDRO-3a, 6, 18, 22-
TETRAACBZACYCLOPENTACYCLODOCOSEN-21-
YL)PROPYL]GUANIDINE

5

COMPOUND 10

Compound 10 was prepared using the general method of Example 1. CBZ-D-PheOH replaced CBZ-D-homophenylalanine in Step 1a and 11-carbobenzoyloxyaminoundecanoic acid replaced 8-carbobenzoyloxyaminooctanoic acid in Step 1c to give the title compound as a solid: FAB-MS m/z 612 (MH^+); Anal Calc'd for $C_{32}H_{49}N_7O_5 \cdot 1.75 H_2O \cdot 1.5 C_2HF_3O_2$:

10

Calc'd: C, 51.62; H, 6.68; N, 12.05; H_2O , 3.93

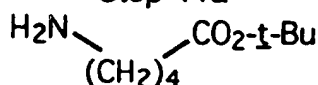
Found: C, 51.83; H, 6.12; N, 11.98; H_2O , 3.93

15

EXAMPLE 11

Preparation of Compound 11

Step 11a

11a

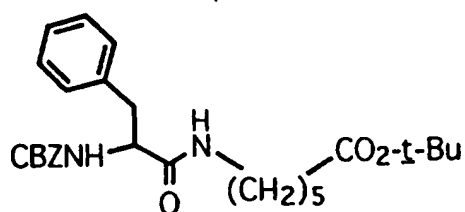
20 Carbobenzoyloxy chloride (271 mL, 1.9 mol) and 4N NaOH (475 mL) were added simultaneously to a solution of 6-aminopentanoic acid (100g, 0.76 mol) in 4 N NaOH (aq.) (190 mL) at such a rate as to maintain the temperature $\leq 10^\circ C$. The reaction was stirred an additional 2 h at $0-5^\circ C$ while the pH was maintained between 10 and 12. The mixture was then diluted with H_2O (250 mL) and extracted four portions of ether (250 mL). The aqueous extract was
25 acidified with 3N H_2SO_4 (pH = 3), and extracted repeatedly with CH_2Cl_2 . The organic extracts were combined and washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo to yield 196 g of 6-carbobenzoyloxyaminopentanoic acid as an oil which solidified upon standing:
30 FAB-MS m/z 266 (MH^+).

A solution of 6-carbobenzoyloxyaminopentanoic acid (50 g) in CH_2Cl_2 (500 mL) was treated with 2.2 mL of H_2SO_4 (conc.), saturated with isobutylene and stirred for 4 h. The resulting mixture was treated with 5% KOH (aq) (200 mL) and the layers were separated. The organic layer was washed twice with
35 brine (2x100 mL), dried (Na_2SO_4) and concentrated. in vacuo. The residue was purified by flash column chromatography (silica gel, hexanes-ether) to

afford 38 g of 6-carbobenzyloxyaminopentanoic acid *t*-butyl ester: MS *m/z* 322 (MH⁺).

A mixture of 6-carbobenzyloxyaminohexanoic acid *t*-butyl ester (9 g, ?? mmol), Pd(OH)₂/C (4.5 g) and 50 mL of ethanol was shaken under 15 psig for 2 h, filtered and concentrated in vacuo to give the amine 11a, as an oil: MS *m/z* 188 (MH⁺). The material was used without further purification.

Step 11b



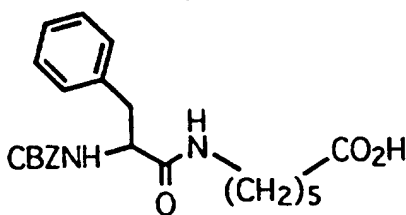
10

11b

A solution of HOBT (4.0 g, 30.2 mmol), DCC (4.6 g, 22.3 mmol) in DMF (35 mL) was added to a solution of amine 11a (4.2 g, 22.2 mmol) and CBZ-D-Phe (6.0 g, 20.0 mmol) in DMF (35 mL). This mixture was stirred overnight, filtered and concentrated in vacuo. The residue was dissolved in CHCl₃, washed sequentially with 10% NaHCO₃ (aq) and brine, dried (Na₂SO₄) and concentrated in vacuo. A 2.0 g portion of the crude residue was purified by flash column chromatography (silica gel, CHCl₃) to afford 1.8 g of the coupled ester 11b: MS *m/z* 469 (MH⁺).

20

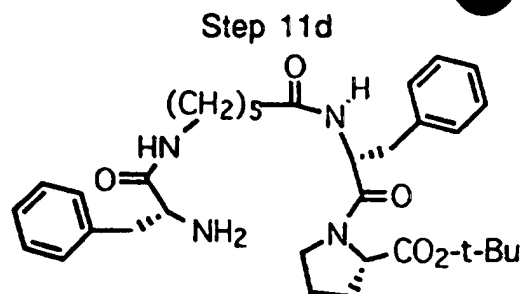
Step 11c



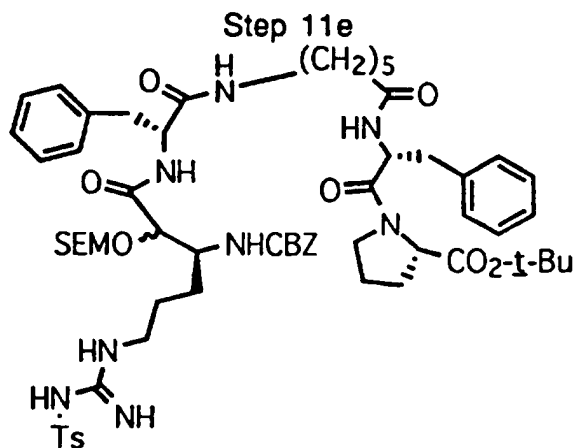
11c

A solution of 11b (2.2 g, 4.7 mmol) in CH₂Cl₂ (5 mL) was added to a solution of 1:1 TFA-CH₂Cl₂ (25 mL) at 0 °C. This solution was gradually warmed to RT and stirred for an additional 1.5 h. The volatiles were removed under a stream of N₂, and the residue was triturated with ether to give the acid 11c as a white solid: (1.8 g); MS *m/z* 413 (MH⁺).

25

**11d**

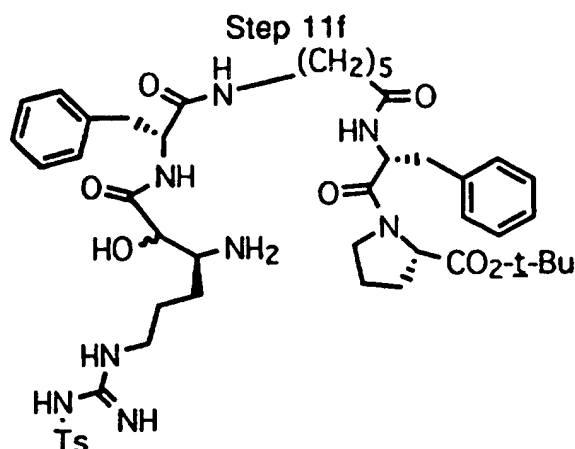
- A solution of DCC (1.1 g, 5.5 mmol) in CH₃CN (5 mL) was added to a stirred solution of **11c** (2.0 g, 5.0 mmol), D-Phe-Pro-O-t-Bu (1.8 g, 5.5 mmol) and HOBT (1.07 g, 7.5 mmol) in CH₃CN (35 mL). This mixture was stirred for 16 h, filtered and concentrated in vacuo. The residue was dissolved in CHCl₃, washed sequentially with 10% NaHCO₃ and brine, dried (Na₂SO₄) and concentrated in vacuo. This residue was purified by flash column chromatography (silica gel, CHCl₃->CHCl₃-MeOH) to give the coupled product as a foam: MS m/z 542 (M - Pro-O-t-Bu)⁺. This material was combined with MeOH (50 mL) and Pd(OH)₂ (1.2 g) and shaken under H₂ (20 psig) for 2.5 h. The reaction was filtered through dicalite and the filter pad thoroughly washed with MeOH. The filtrate was concentrated to give intermediate **11d** as a foam: (1.8 g); MS 579 (MH⁺).

**11e**

- A solution of 6-[[imino[4-methylbenzenesulfonyl] amino]methyl]amino]-2-(R,S)-[[2-(trimethylsilyl)ethoxy]methoxy]-3(S)-[9-phenylmethoxycarbonyl]-amino]hexanoic acid, (1.0 g, 1.6 mmol) of **11d** (1.0 g, 1.8 mmol) and HOBT (0.3 g, 2.2 mmol) in CH₃CN (35 mL) was treated with a solution of DCC (0.4 g, 1.8 mmol) in CH₃CN (5 mL) and stirred overnight. The mixture was filtered and the filtrate was concentrated in vacuo. The residue was dissolved in CHCl₃,

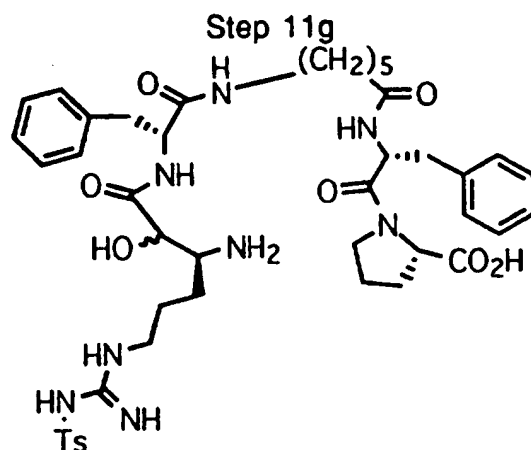
washed successively with 10% Na₂CO₃ and H₂O, dried (Na₂SO₄) and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, CHCl₃ -> CHCl₃.MeOH) to give the arginine derivative 11e as a solid: (1.5 g); MS m/z 1184 (MH⁺).

5



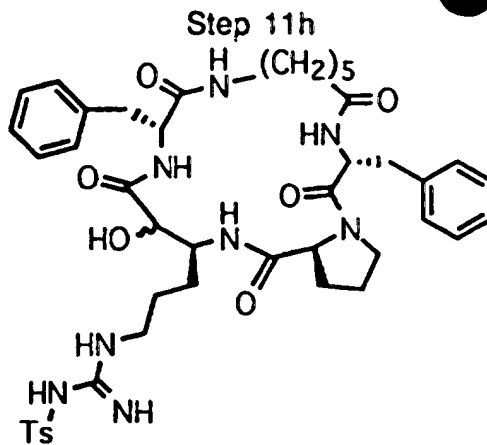
11f

A mixture of **11e** (1.5 g, 1.26 mmol), Pd(OH)₂ (0.8 g) and MeOH (50 mL) was shaken under H₂ at 20 psig for 2.5 h. The mixture was filtered and the filtrate was concentrated in vacuo to give the deprotected intermediate **11f** 1.2 g as an off white solid: MS m/z 1049 (MH⁺).

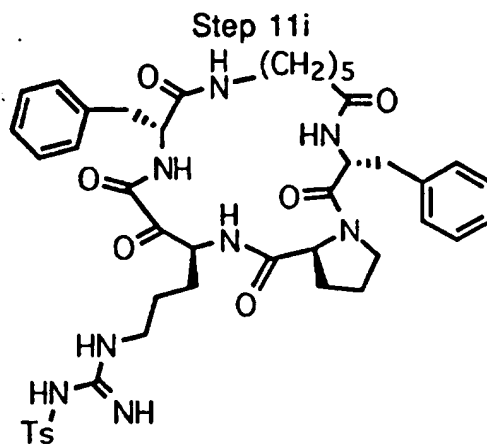


11g

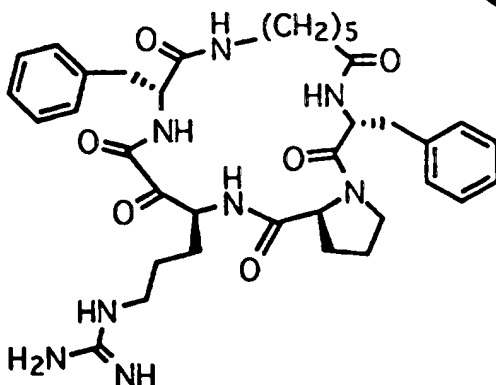
To a solution of 1:1 TFA-CH₂Cl₂ (15 mL) was added to a solution of **11h** (1.24 g, 1.2 mmol) in CH₂Cl₂ (5 mL) at 0 °C. This mixture was stirred for 2.5 h at room temperature, and the volatiles were removed under a stream of N₂. The residue was triturated with ether and collected to afford **11g**, 1.1 g as a white solid: MS 863 (MH⁺).



A mixture of **11g** (1.1 g, 1.1 mmol) in CH_2Cl_2 (1.1L) was treated with DMAP (0.7 g, 5.7 mmol) followed by BOP-Cl (0.6 g, 2.3 mmol). This mixture was stirred for 24 h, then concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 , washed with 10% citric acid (aq), dried (Na_2SO_4) and concentrated. *in vacuo*. The residue was purified by flash column chromatography (silica gel, $\text{CH}_2\text{Cl}_2 \rightarrow 95\% \text{CH}_2\text{Cl}_2\text{-MeOH}$ to yield **11h**, (0.3 g) as a solid: MS 845 (MH^+).



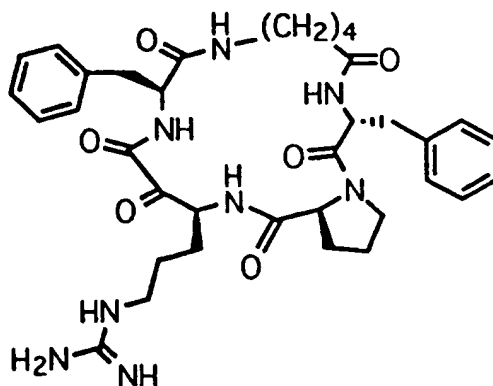
Intermediate **11h** (0.3 g, 0.3 mmol) was added to a mixture of Dess-Martin periodinane (2.0 g, 0.5 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred for 1.5 h, and treated with an excess of 10% $\text{Na}_2\text{S}_2\text{O}_3$ (aq) in NaHCO_3 (satd. aq.). The layers were separated, and the aqueous layer was extracted three times with CHCl_3 . The combined organic extracts were washed with H_2O , dried (Na_2SO_4), and concentrated *in vacuo* to give **11i** (0.3 g) as a white solid which was used without purification.



5R, 15R, 19S, 21AS-N-[3-(5, 15-DIBENZYL-4, 7, 14, 17, 18, 21,
HEXAOXOEICOSAHYDRO-3a, 6, 16, 20-
PENTAAZACYCLOPENTACYCLOEICOSEN-19-
YL)PROPYL]GUANIDINE TRIFLUOROACETATE
COMPOUND 11

A mixture of intermediate 11i (0.3 g) and anisole (6 mL) was treated with HF (ca. 10 mL) at -78°C, and warmed to 0°C. This mixture was stirred for 4.5 h and the HF was removed in vacuo. The residue was triturated with ether and the resulting solid was purified by reverse phase HPLC (1:1 0.2 CH₃CN-H₂O-TFA) to afford the title compound (0.1 g) as a white powder: MS 620 (MH⁺); Anal. Calc'd for C₂₃H₄₅N₇O₅•1.75 C₂HF₃O₂•1.5 H₂O:
Calc'd: C, 51.14; H, 5.63; N, 11.93; H₂O, 2.40.
Found: C, 51.19; H, 5.70; N, 12.08; H₂O, 2.59.

EXAMPLE 12



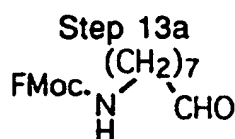
5R, 15S, 19S, 21a-S-N-[3-(5, 15-DIBENZYL-4, 7, 14, 17, 18, 21-
HEXAOXODOCOSAHYDRO-3a, 6, 13, 16, 20-
PENTAAZACYCLOPENTACYCLOEICOSEN-19-
YL)PROPYL]GUANIDINE TRIFLUOROACETATE
COMPOUND 12

Compound 12 was prepared following the method of Example 11. *N*- α -CBZ-L-Phe was used in place of *N*- α -CBZ-D-Phe in Step 11b and all other steps were carried out with only minor modifications: Anal calc'd for C₃₆H₄₈N₈O₆•1.35 C₂H₅F₃O₂•2.0 H₂O:

5 Calc'd: C, 52.89; H, 6.12; N, 12.75; H₂O, 4.10
 Found: C, 53.02; H, 5.92; N, 12.82; H₂O, 3.97

EXAMPLE 13

5R, 18S, 20a-S - N - [3-(5-BENZYL-4, 16, 17, 20-
 10 TETRAOXOEICOSAHYDRO-3a, 6, 15, 19-
 TETRAAZACYCLOPENTACYCLONONADECEN-18-YL) PROPYL]
 GUANIDINE TRIFLUOROACETATE

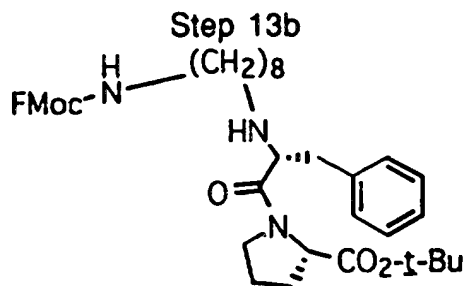


15

13a

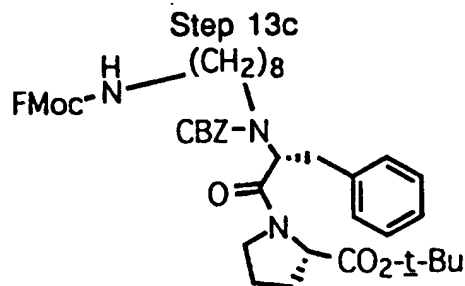
Fluorenylmethoxycarbonyl chloride (4.87 g, 0.02 mol) to a mixture of aminooctanoic acid (3.0 g, 0.02 mol) in 200 mL of 10% Na₂CO₃ (aq) and dioxane (150 mL) at 0°C. The mixture was stirred for 2.5 h at 0°C, acidified to pH 5 with acetic acid and extracted three times with CHCl₃. The combined
 20 organic extracts were washed with H₂O, dried (Na₂SO₄) and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, CHCl₃-> 95:5 CHCl₃-MeOH) to afford 8-fluorenylmethoxycarbonylamino octanoic acid (6.4 g) as a solid: MS 382 (MH⁺). The product was dissolved in CH₂Cl₂ (40 mL), cooled to 0°C, and treated with
 25 methoxymethyl amine hydrochloride (2.05 g, 21.1 mmol), triethylamine (8.1 mL) and BOP reagent (8.0 g). This mixture was stirred for 12 h at 0°C, washed sequentially with 3N HCl, NaHCO₃ (sat'd. aq.) and brine. The organic phase was dried (Na₂SO₄) and concentrated. in vacuo. The residue was purified by flash column chromatography (silica gel; CHCl₃->98:2 CHCl₃-MeOH) to afford
 30 8-fluorenylmethoxycarbonyl-amino octanoic acid N,N-methoxymethyl amide (7.1 g): MS m/z 425 (MH⁺). A solution of the product (6.8 g) in THF (80 mL) was cooled to -40°C and treated dropwise with 1.0 M DIBAL/THF (48.5 mL). The mixture was stirred an additional 15 min, quenched with 3N HCl (50 mL) and warmed to room temperature. The resulting aqueous layer was extracted
 35 repeatedly with CHCl₃ and the combined organic extracts were washed with brine, dried (Na₂SO₄) and concentrated in vacuo. The residue was purified by

chromatography (silica gel; CH₂Cl₂→2% MeOH-CH₂Cl₂) to afford aldehyde 13a as a solid: 5.2 g; MS m/z 366 (MH⁺).



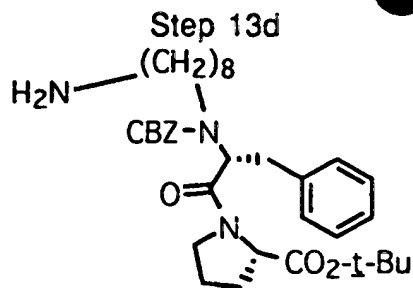
13b

A solution of 13a (4.2 g, 11.6 mmol) and D-Phe-Pro-O-t-Bu (4.1 g, 12.7 mmol) in CH₂Cl₂ (100 mL) was treated with sodium triacetoxy borohydride (3.7 g, 17.4 mmol), followed by glacial acetic acid (0.7 g). This mixture was stirred for 3.5 h, treated with excess NaHCO₃ (sat'd) and the resulting aqueous layer was extracted repeatedly with CH₂Cl₂. The combined organic layers were washed with brine, dried (Na₂SO₄), and concentrated in vacuo to give the coupled product 13b as a semi-solid: 7.8 g; MS m/z 668 (MH⁺).

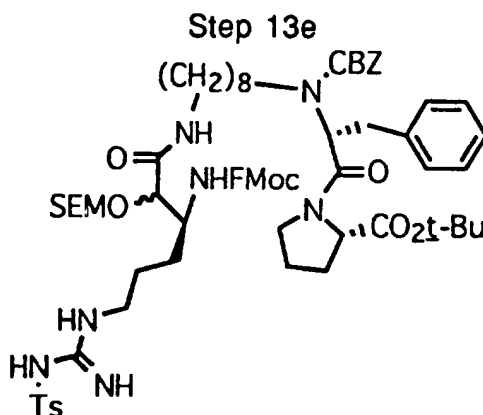


13c

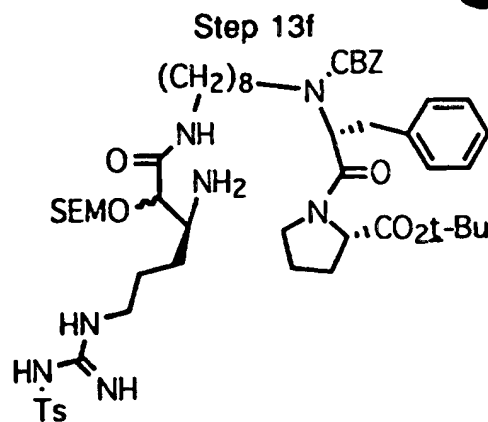
A mixture of 13b (7.8 g, in 1:1 CH₂Cl₂ -H₂O (30 mL) was cooled to 0 °C and treated with NaHCO₃ (1.1 g, 12.7 mmol) of followed by dropwise addition of benzylchloroformate (1.8 mL, 12.7 mmol). This mixture was stirred for 2h at 0 °C, and the aqueous phase was extracted repeatedly with CH₂Cl₂. The combined organic layers were washed sequentially with H₂O and brine, dried (Na₂SO₄) and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, CHCl₃) to give 13c as a semi-solid: 7.3 g; MS m/z 802 (MH⁺).

**13d**

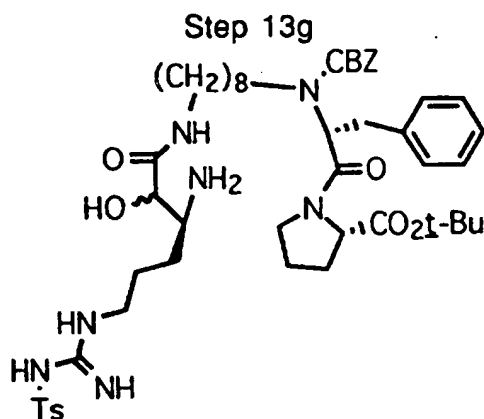
A solution of **13c** (2.4 g) in DMF (20 mL) was treated with piperidine 4 mL and stirred for 25 min. The resulting mixture was concentrated *in vacuo* and triturated with hexane to give **13d** as an oil: 1.5 g; MS m/z 580 (MH⁺).

**13e**

A solution of 6-[[imino[4-methylbenzenesulfonyl] amino]methyl]amino]-2-(R,S)-[[2-(trimethylsilyl)ethoxy]methoxy]-3(S)-[9-fluorenylmethoxycarbonyl]-amino]hexanoic acid (1.6 g, 2.3 mmol), **13d** (1.4 g, 2.5 mmol), and HOBT (0.46 g, 3.4 mmol) in CH₃CN (35 mL) was treated with a solution of DCC (0.51 g, 2.5 mmol) in CH₃CN (5 mL). This mixture was stirred for 12 h, filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, CHCl₃->5% MeOH-CHCl₃) to afford **13e** as a semi solid: 1.8 g; MS m/z 1273 (MH⁺)

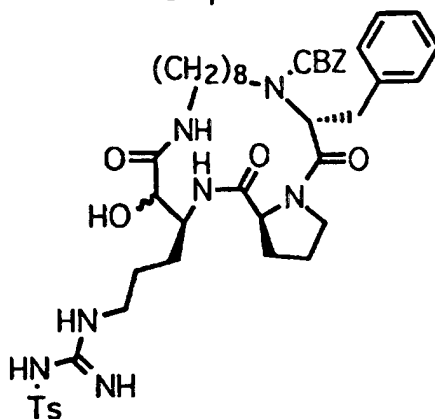


- 5 Piperidine (4 mL) was added to a solution of **13e** (1.7 g) in DMF (20 mL) and stirred for 30 min. This mixture was concentrated in vacuo and the residue was washed with hexanes to yield **13f** as an oil: 1.4 g; MS m/z 1050 (MH⁺)

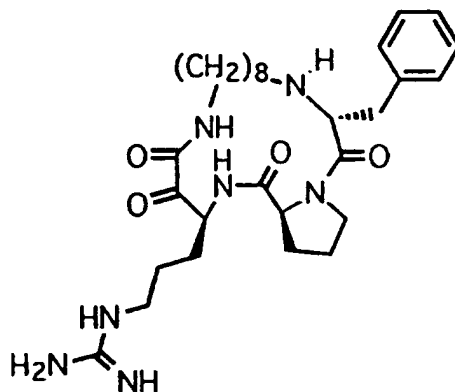


- 10 A solution of TFA (15 mL) and CH₂Cl₂ (10 mL) was added a solution of **13f** (1.4 g) in CH₂Cl₂ (5 mL) at 0 °C. This mixture was warmed to room temperature and stirred for 2 h. The volatiles were removed under a stream of N₂ and the residue was triturated with ether to afford **13g** as a solid: 1.1 g; MS m/z 864
- 15 (MH⁺).

Step 13h

13h

BOP-Cl (0.5 g, 2.0 mmol) was added to a solution of 13g (1.1 g, 1.0 mmol) and
 5 DMAP (0.63 g, 5.2 mmol) in CH₂Cl₂ (1.0 L). This mixture was stirred for 6 h and
 concentrated in vacuo. The residue was purified by flash column
 chromatography (silica gel; 5% MeOH-CH₂Cl₂) to afford 13h as a white foam:
 0.31 g; MS m/z 846 (MH⁺).



10

5R, 18S, 20a-S - N - [3-(5-BENZYL-4, 16, 17, 20-
 TETRAOXOEICOSAHYDRO-3a, 6, 15, 19-
 TETRAAZACYCLOPENTACYCLONADECEN-18-YL) PROPYL]
 GUANIDINE TRIFLUOROACETATE

15

COMPOUND 13

A suspension of 13e (0.2 g, 0.4 mmol) in CH₂Cl₂ (10 mL) was treated with (0.3
 g, 0.6 mmol) of the Dess-Martin periodinane and stirred for 2 h. The mixture
 was treated with excess solution of 25% Na₂S₂O₃ in NaHCO₃ (sat'd aq.) and the
 the aqueous layer was extracted repeatedly with CH₂Cl₂. The combined
 20 organic extracts were washed with water, dried (Na₂SO₄) and concentrated
in vacuo to yield the keto-amide product (0.3 g) which was used in the next step
 without purification: MS m/z 844 (MH⁺). A stirred mixture of the keto-amide and

anisole (3 mL) was treated with HF (ca. 15 mL) at -78°C. This mixture was stirred an additional 3.5 h at 0 °C, and the HF was removed in vacuo at 0 °C. The residue was triturated with ether, and the residue was purified by reverse-phase HPLC (30:70:0.2 CH₃CN-H₂O-TFA). The desired fractions were

5 lyophilized to give the title compound as a white solid : 0.1 g; MS m/z 556.5

(MH⁺); Anal. Calcd for C₂₉H₄₅N₇O₄•2.75 C₂HF₃O₂•1.25 H₂O

Calc'd: C, 46.46; H, 5.68; N, 10.99; H₂O, 2.47

Found: C, 46.53; H, 5.72; N, 11.15; H₂O, 2.77.

10

EXAMPLE 14

2S, 5S, 9R-N[3-(9-BENZYL-3, 6, 7, 10, 19-

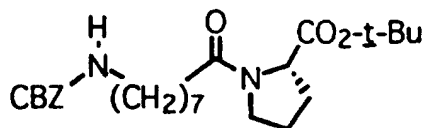
(PENTAOXOEICOSAHYDRO)-1a, 4, 8, 11-

(TETRAAZACYCLOPENTACYCLONONADECEN-5-

YL)PROPYL] GUANIDINE TRIFLUOROACETIC ACID.

15

Step 14a



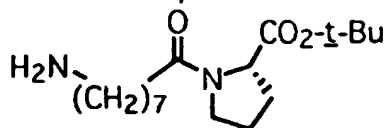
14a

20

A solution of N-α-Cbz-aminooctanoic acid (2.5 g, 8.5 mmol), Pro-O-t-Bu (1.6 g, 9.4 mmol) and HOBt (1.7 g, 12.8 mmol) in CH₃CN (80 mL) was added a solution of DCC (1.4 g, 9.4 mmol) in CH₃CN. (15 mL). The reaction was stirred overnight, filtered and the resulting filtrate concentrated in vacuo. The residue was purified by flash column chromatography CH₂Cl₂ -> 2% MeOH-CH₂Cl₂) to afford **14a** :3.8 g; MS m/z 447 (MH⁺).

25

Step 14b

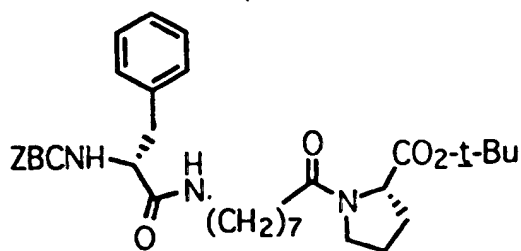


14b

30

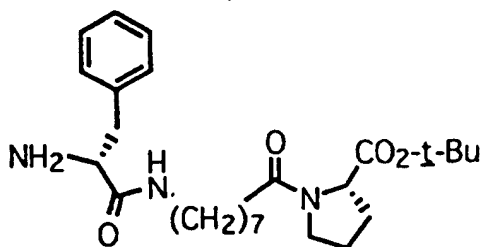
A mixture of **14a** (3.6 g), Pd(OH)₂ (1.8 g) in MeOH (75 mL) was shaken under H₂ (20 psig) for 2.5 h. This mixture was filtered, and the filtrate was concentrated in vacuo to give the free amine **14b** (2.5 g) which was used without further purification.

Step 14c

14c

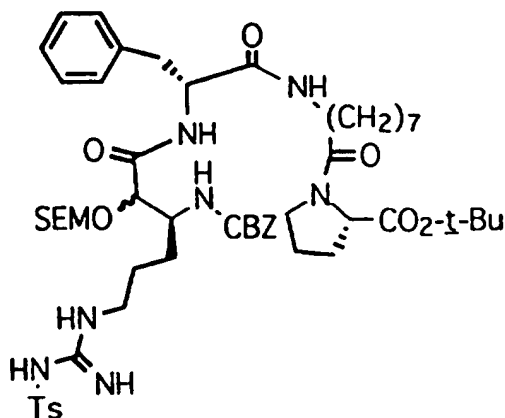
- A solution of N- α -Cbz-D-Phe (2.2 g, 7.3 mmol) of, 14c (2.5 g, 8.1 mmol) and HOBT (1.4 g, 11.0 mmol) in CH₃CN (10 mL) was treated with DCC (1.7 g, 8.1 mmol) in CH₃CN (10 mL). The mixture was stirred overnight, filtered and the filtrate was concentrated in vacuo. The residue was dissolved in CHCl₃, washed with NaHCO₃ (sat'd. aq), dried (Na₂SO₄) and concentrated in vacuo. This residue was purified by flash column chromatography (silica gel, 97:3 CHCl₃-MeOH) to afford 14c: 3.7 g; MS m/z 594 (MH⁺).

Step 14d

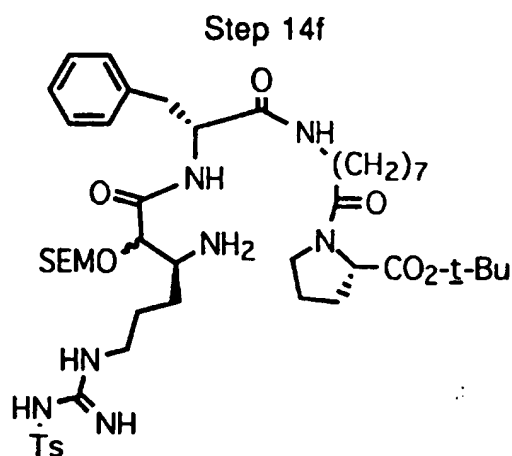
14d

- A mixture of 14c (3.7 g), MeOH (75 mL) and PdOH₂ (1.4 g) was shaken under H₂ (20 psig) for 2.5 h and filtered. The filtrate was concentrated in vacuo to afford 14d (2.5 g) which was used in the next step without purification.

Step 14e

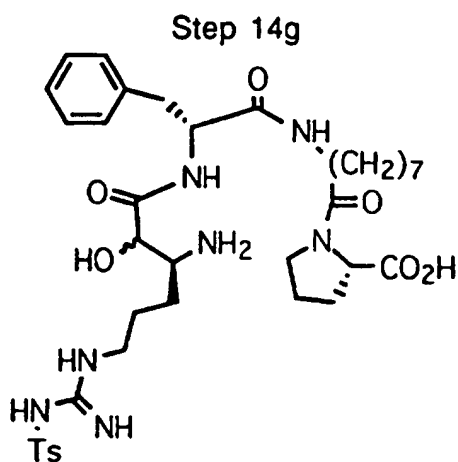
14e

A mixture of 6-[[[imino[4-methylbenzenesulfonyl] amino]methyl]amino]-2-(R,S)-[[2-(trimethylsilyl)ethoxy]methoxy]-3(S)-[9-phenylmethoxycarbonyl]-amino]hexanoic acid (1.0 g, 1.6 mmol), **14d** (0.81 g, 1.8 mmol) and HOBT (0.32 g, 2.4 mmol) of HOBT in CH₃CN (60 mL) was treated with DCC (0.36 g, 1.8 mmol) in CH₃CN (60 mL). This mixture was stirred overnight, filtered and the resulting filtrate was concentrated in vacuo. The residue was dissolved in CHCl₃, washed with 10% aqueous Na₂CO₃, dried (Na₂SO₄) and concentrated in vacuo. This residue was purified by flash column chromatography (silica gel, CHCl₃->98% CHCl₃-MeOH) to afford **14e** (1.42 g) as a white solid: MS m/z 1064 (MH⁺).



14f

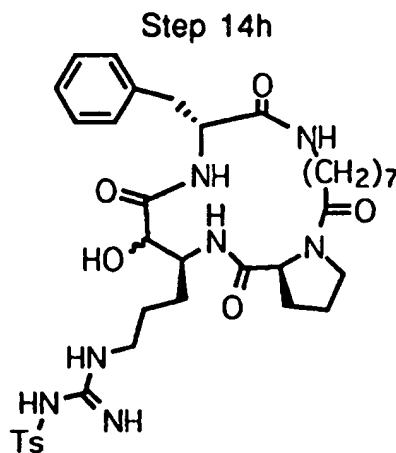
15 A mixture of **14e** (1.42 g) Pd(OH)₂ (0.8 g) and MeOH (50 mL) under H₂ (20 psig) for 2.5 h. This mixture was filtered, and the filtrate concentrated in vacuo to yield amine **14f** (1.18 g) : MS m/z 930 (MH⁺).



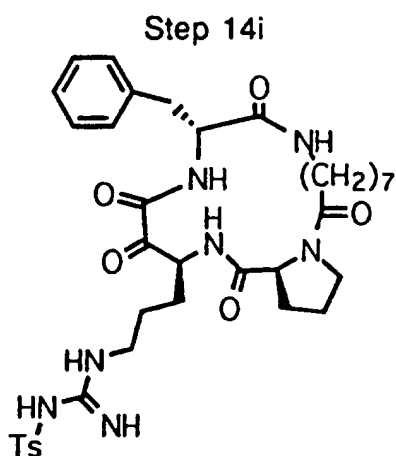
14g

A solution of 14g (1.18 g) in CH₂Cl₂ (5 mL) was added to a solution of 1:1 TFA-CH₂Cl₂ (20 mL) at 0 °C. This mixture was stirred for 2 h at room temperature and the solvent was removed under a stream, of N₂. The residue was triturated with ether to afford 14g (1.02 g) which was used without additional purification.

5



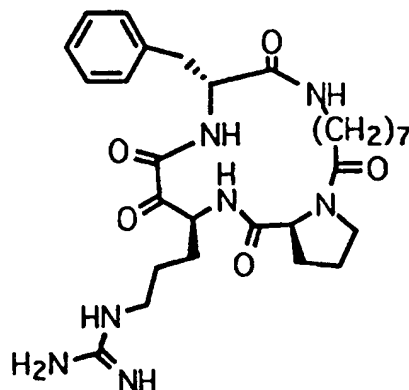
- A solution of 14h (1.01 g, 1.18 mmol) in CH₂Cl₂ was treated with DMAP (0.73 g, 6.0 mmol) followed by BOP-Cl (0.60 g, 2.35 mmol). This mixture was stirred for 24 h and the total volume was reduced to 100 mL in vacuo. This solution was washed with 10% aqueous citric acid, dried (Na₂SO₄) and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, CH₂Cl₂ -> 10% MeOH-CH₂Cl₂) to yield 14h (0.30 g)



- A solution of 14i (0.30 g, 0.42 mmol) in CH₂Cl₂ (10 mL) was added to a suspension of Dess-Martin periodinane (0.26 g, 0.62 mmol) in CH₂Cl₂ (10 mL). After 2.5 h, the mixture was treated with an excess of 25% Na₂S₂O₄ (aq) in

NaHCO₃ (sat'd. aq) and stirred for 5 min. The aqueous layer was extracted with CH₂Cl₂ and the combined organic extracts were washed with H₂O, dried (Na₂SO₄) and concentrated under in vacuo to afford 14i (0.30 g) which was used in the next step without purification: MS m/z 724 (MH⁺).

5



2S, 5S, 9R-N[3-(9-BENZYL-3, 6, 7, 10, 19-
(PENTAOXOEICOSAHYDRO)-1a, 4, 8, 11-
(TETRAAZACYCLOPENTACYCLONONADECEN-5-
YL)PROPYL] GUANIDINE TRIFLUOROACETIC ACID

10

COMPOUND 14

A suspension of 14i (0.30 g) in anisole (2 mL) was cooled to -78°C and treated with anhydrous HF (ca. 10 mL) using a standard HF apparatus. This mixture was stirred for 4h at 0 °C and the HF was removed in vacuo at 0°C. This residue was triturated twice with ether (2 X 25 mL) and the resulting solid was purified by reverse-phase HPLC (MeCN-water-TFA, 40:60:0.2). Lyophilization of the eluate provided the title compound (0.44 g) as a white solid : FAB-MS m/z 570 (MH⁺)

15

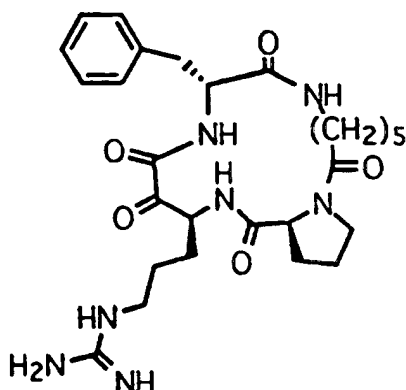
Anal. Calc'd for C₂₉H₄₃N₇O₅•1.25 C₂HF₃O₂•2.0 H₂O

20

Calc'd: C, 50.56; H, 6.50; N, 13.10; H₂O, 4.82.

Found: C, 50.31, H, 6.25; N, 12.70; H₂O; 4.33.

EXAMPLE 15

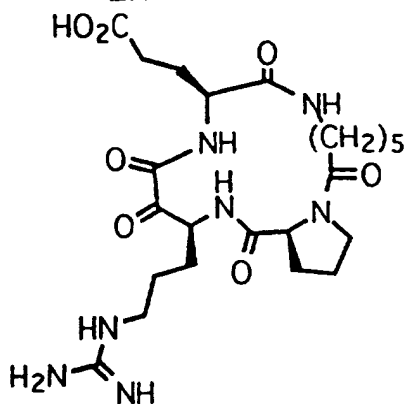


12R,16S,19S-N-[3-(12-BENZYL-4,11,14,15,18-PENTAOXOOCTADECALHYDRO)-
 3a,10,13,17-(TETRAAZACYCLOPENTACYCLOHEPTADECEN-16-YL)PROPYL]-
 5 GUANIDINE TRIFLUOROACETIC ACID
 COMPOUND 15

The preparation of compound 15 is analogous to Example 14. The hexanoyl
 analog of 14d, namely 1(S)-[6-(2(R)-amino-3-
 phenylpropionylamino)hexanoyl]pyrrolidine-2-carboxylic acid *t*-butyl ester, was
 10 prepared by coupling CBZ-D-Phe with 6-aminohexanoic acid *t*-butyl ester,
 saponifying the ester and coupling the resulting acid with Pro-O-*t*-Bu. The
 remaining steps of Example 14 were carried out to give the title compound as a
 solid: FAB-MS *m/z* 542 (MH⁺); Anal Calc'd. for C₂₇H₃₉N₇O₅•1.75 CF₃CO₂H•1.5
 H₂O:

15 Calc'd: C, 47.69; H, 5.74; N, 12.76; H₂O, 3.53
 Found: C, 47.81; H, 5.74; N, 13.04; H₂O, 3.57.

EXAMPLE 16



20 12S,16S,19S-3-[16-(3-GUANIDINOPROPYL)-4,11,14,15,18-
 PENTAOXOOCTADECALHYDRO-3,10,13,17-
 TETRAAZACYCLOPENTACYCLOHEPTADECEN-1,2-YL]PROPIONIC ACID
 TRIFLUOROACETATE

COMPOUND 16

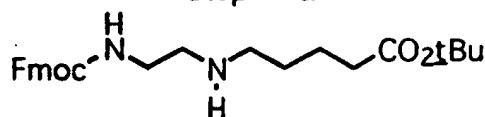
The preparation of compound 16 is analogous to Example 14. The hexanoyl analog of 14d, namely 1(S)-[6-(2(R)-amino-3-(carboxymethyl)propionylamino)hexanoyl]pyrrolidine-2-carboxylic acid *t*-butyl ester, was prepared by coupling L-N- α -Fmoc-Glu(OBzl)-OH with 6-aminohexanoic acid *t*-butyl ester, saponifying the ester and coupling the resulting acid with Pro-O-*t*-Bu. The remaining steps of Example 14 were carried out to give the title compound as a solid: FAB-MS *m/z* 523 (MH⁺); Anal Calc'd. for C₂₃H₃₇N₇O₇•2.0CF₃CO₂H•1.5 H₂O:

- 10 Calc'd: C, 41.65; H, 5.44; N, 12.59; H₂O, 3.47
 Found: C, 41.83; H, 5.30; N, 12.64; H₂O, 3.57.

EXAMPLE 17

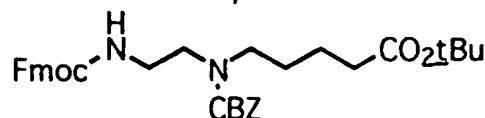
- 15 5R,18S,21S-N-[3-(4,7,16,17,20-PENTAOXO-5-PHENETHYLEICOSAHYDRO-3a, 6, 15, 19-TETRAACBZACYCLOPENTACYCLONONADECEN-18-
 YL)PROPYL]GUANINDINE TRIFLUOROACETIC ACID

Step 17a

17a

- 20 Sodium Triacetoxymethylborohydride (6.1 g, 29 mmol) and acetic acid (1 mL) were added to a solution of N- α -(fluorenylmethyloxycarbonyl)glycinal (5.4 g, 19 mmol: prepared by the method of Ho, et al. *Journal Of Organic Chemistry* 1983, 58, 2313-16) and 5-aminopentanoic acid *t*-butyl ester (3.6 g, 20 mmol) in CH₂Cl₂ (30 mL). This mixture was stirred overnight and concentrated in vacuo
 25 to give 17a which was used without purification

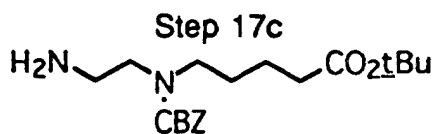
Step 17b

17b

- 30 To a solution of 11 g of intermediate 3 and 5.6 mL of triethylamine in 150 mL of CH₂Cl₂ at 0 °C Carbobenzoylchloride (3.1 mL) was added to a stirred solution of 14a (11g) and triethylamine (5.6 mL) in CH₂Cl₂ (150 mL). After 2 h, the reaction was quenched with H₂O, and the resulting organic layer was extracted twice with CH₂Cl₂. The combined organic layers were dried (Na₂SO₄) and
 35 concentrated. The residue was purified by flash chromatography (silica gel; 3:1

hexanes-ether-> 3:2 hexanes-ether) to afford 2.6 g of 17b as a white solid: MS m/z 573 (MH⁺).

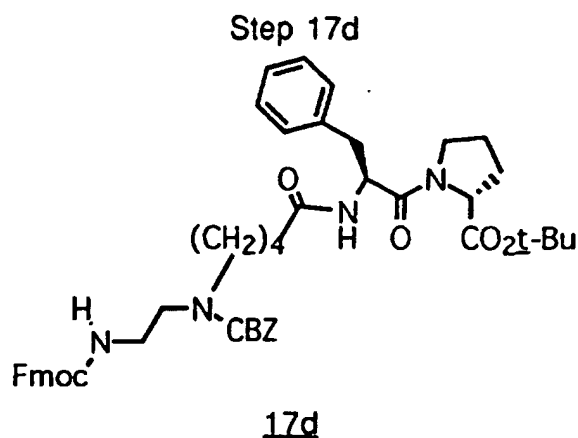
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10

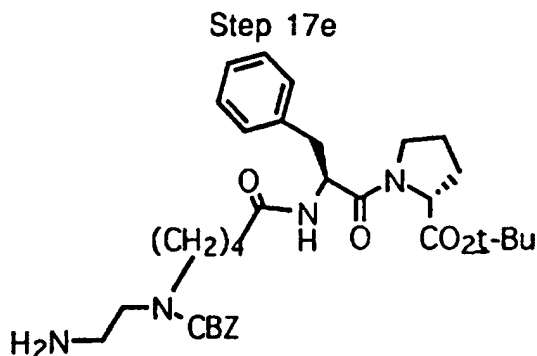
A solution of intermediate 17b (2.42 g) in CH₂Cl₂ (5 mL) was added to a 1:1 solution of TFA-CH₂Cl₂ (20 mL) at 0 °C. The reaction was stirred for 1 h at room temperature, then volatiles were removed under a stream of N₂ at room temperature. The residue was purified by chromatography (flash column, silica gel; 9:1 CHCl₃-MeOH) to afford 1.8 g of 17c: MS m/z 517 (MH⁺).

15



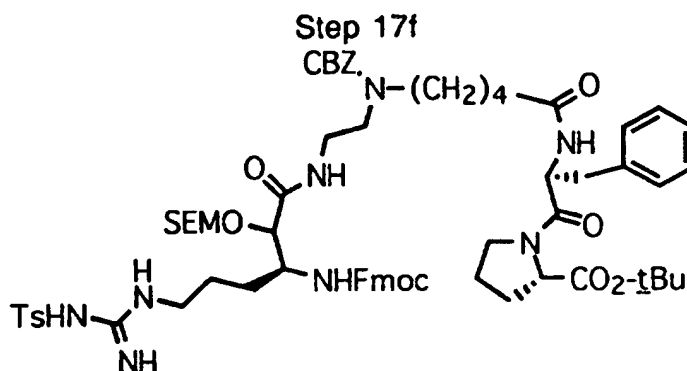
20

A solution of 17c (1.72 g, 3.33 mmol) and D-Phe-Pro-O-t-Bu (1.58 g, 4.99 mmol) and HOBT (0.67 g, 4.99 mmol) was treated with a solution of DCC (1.03 g, 5.00 mmol) in CH₃CN (3 mL) and stirred overnight. The mixture was filtered and concentrated, and the residue was purified by flash chromatography (silica gel, 100 % CHCl₃ -> 98% CHCl₃-MeOH) to give 2.28 g of intermediate 17d: MS m/z 817 (MH⁺).



17e

A solution of 17d (2.24 g) in CH₃CN (25 mL) was treated with diethylamine (6 mL) and the mixture was stirred for 2.5 h. The solution was concentrated in vacuo, and the residue was purified by flash chromatography (silica gel, 100 % CHCl₃ -> 90% CHCl₃-MeOH) to give 1.27 g of intermediate 17e: MS m/z 595 (MH⁺).

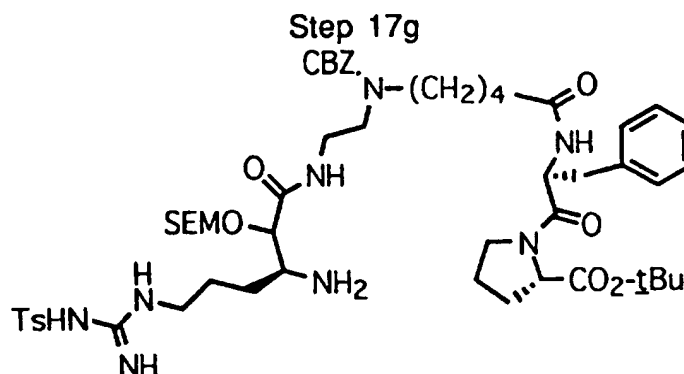


10

17f

To a stirred solution of [[imino[4-methylbenzenesulfonyl)amino]methyl]amino]-2-(R,S)-[[2-(trimethylsilyl)ethoxy]methoxy]-3(S)-[9-fluorenylmethoxycarbonyl)-amino]hexanoic acid, (2.5 g, 4.0 mmol: prepared analogous to the CBZ derivative in Maryanoff et al. *Journal of the American Chemical Society* 1995, 117, 1225-39) and intermediate 17f (1.27 g, 2.13 mmol) and HOBT (0.39 g, 2.91 mmol) in CH₃CN (45 mL) was added DCC (0.44 g, 2.13 mmol) and this mixture was stirred overnight. The reaction was filtered, the filtrate was concentrated, and the residue was purified by flash chromatography (silica gel, 100 % CHCl₃ -> 95% CHCl₃-MeOH) to yield 1.96 g of intermediate 17f: MS m/z 1287 (MH⁺).

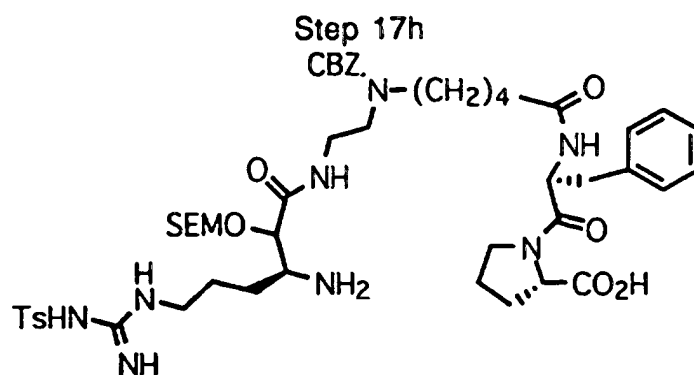
20

17g

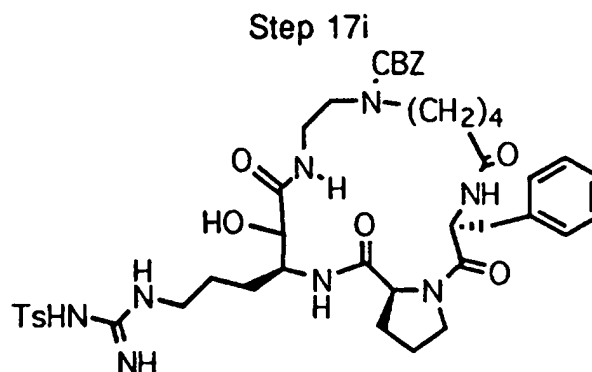
A solution of intermediate 17g (1.93 g) in CH₃CN (20 mL) was treated with diethylamine (5 mL) and stirred for 2h. The solution was concentrated, and the

25

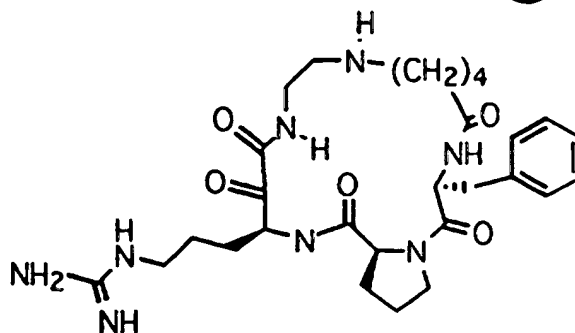
residue was triturated repeatedly with ether to afford 1.31 g of intermediate 17g : MS m/z 1065 (MH+).



To a solution of 1:1 TFA -CH₂Cl₂ (20 mL) at 0 °C was added a solution of intermediate 17g (1.31 g, 1.23 mmol) in CH₂Cl₂ (5 mL). After stirring at room temperature for 1h, the solution was concentrated under a stream of N₂, and the residue was triturated with ether to afford 1.1 g of intermediate 17h as a white solid: MS m/z 879 (MH+).



A mixture of intermediate 17h (1.1 g, 1.0 mmol) and DMAP (0.63 g, 5.1 mmol) in CH₂Cl₂ (1 L) was treated with BOP-Cl (0.51 g, 2.0 mmol) and stirred for 4 h. The mixture was reduced ca. 75%, washed twice with 10% aqueous citric acid, dried (Na₂SO₄) and concentrated. The residue was purified by flash column chromatography (silica gel, CH₂Cl₂-> 10% MeOH-CH₂Cl₂) to give 0.53 g of intermediate 17i : MS m/z 861 (MH+).



5R,18S,21S-N-[3-(4,7,16,17,20-PENTAOXO-5-PHENETHYLEICOSAHYDRO-
3a, 6, 15, 19-TETRAAZACYCLOPENTACYCLONONADECEN-18-
YL)PROPYL]GUANINDINE TRIFLUOROACETIC ACID

5

COMPOUND 17

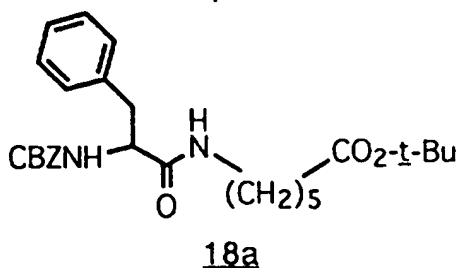
To a mixture of Dess-Martin periodinane (0.39 g, 0.89 mmol) in CH_2Cl_2 (10 mL) was added to a solution of intermediate 17i (0.51 g) in CH_2Cl_2 (10 mL). After stirring for 1h, the reaction was treated with excess 25% $\text{Na}_2\text{S}_2\text{O}_3(\text{aq})$ in NaHCO_3 (sat'd., aq.) and the layers were separated. The aqueous layer was
10 extracted three times with CHCl_3 , and the combined organic layers were washed with water, dried (Na_2SO_4), and concentrated in vacuo to afford 0.46 g of the corresponding keto-amide: MS m/z 859 (MH^+). A mixture of the keto-amide (0.44 g) in anisole (3 mL) was treated with ca. 10 mL of HF at -78°C and stirred at 0°C for 3.5 h. Excess HF was removed under in vacuo at 0°C ,
15 and the residue was triturated twice with ether. The residue was purified by reverse-phase HPLC (80:20:0.2 $\text{H}_2\text{O}-\text{CH}_3\text{CN}-\text{TFA}$) to afford 0.052 g of the title compound as a white solid: MS m/z 571.5 (MH^+); mp $102-106^\circ\text{C}$; Anal. Calcd. for $\text{C}_{28}\text{H}_{42}\text{N}_8\text{O}_5 \cdot 2.5 \text{ C}_2\text{HF}_3\text{O}_2 \cdot 3.5 \text{ H}_2\text{O}$:
Calculated C, 43.14; H, 5.65; N, 12.20; H_2O , 6.86;
20 Found: C, 42.91; H, 5.38; N, 12.42; H_2O , 6.44.

EXAMPLE 18

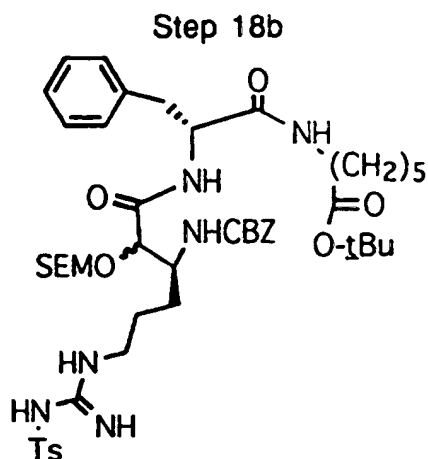
N-[3-(3-BENZYL-2,5,6,9-TETRAOXO-1,4,8-TRIAZACYCLOTETRADEC-
7-YL)PROPYL]GUANINDINE TRIFLUOROACETIC ACID

25

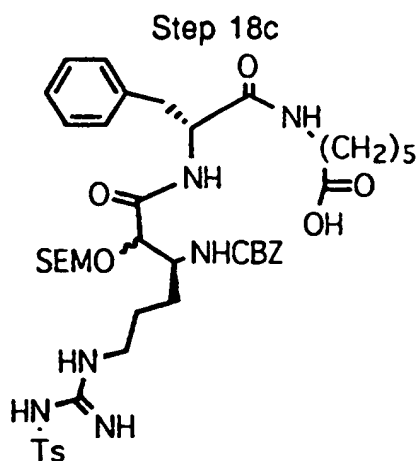
Step 18a



Intermediate **18a** was prepared following steps 11a and 11b of example by using 6-aminohexanoic acid instead of aminopentanoic acid in step 11a.



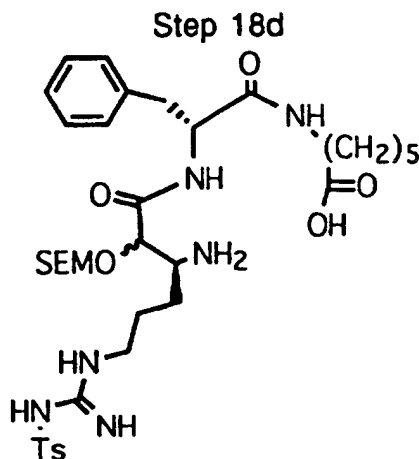
A mixture of **18a** (0.72 g, 2.15 mmol), 6-[[[imino[4-methylbenzenesulfonyl]amino]methyl]amino]-2-(R,S)-[[2-(trimethylsilyl)ethoxy]methoxy]-3(S)-[9-phenylmethoxycarbonyl]-amino]hexanoic acid (1.47 g, 2.36 mmol) and HOBT (0.44 g, 3.22 mmol) dissolved in CH₃CN (30 mL) was treated with a solution of DCC (0.49 g, 2.36 mmol) in CH₃CN (30 mL) and stirred overnight. The mixture was filtered, concentrated in vacuo and the residue was dissolved in mL ethyl acetate (50 mL) and washed with saturated aqueous NaHCO₃ (5 mL). The organic extract was dried (Na₂SO₄) and concentrated. The residue was purified via flash column chromatography (9:1 CH₂Cl₂-MeOH) to yield 1.72 g of intermediate **18b**.



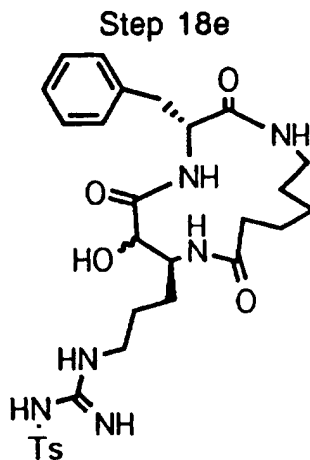
20

A solution of intermediate **18b** (1.71 g, 1.82 mmol) in CH₂Cl₂ (5 mL) was added to 1:1 TFA-CH₂Cl₂ (28 mL) solution at 0 °C. The mixture was stirred for 1 h at

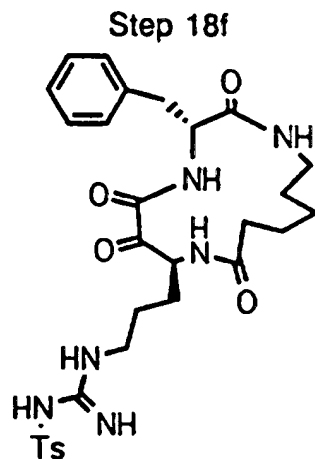
room temperature and concentrated under a stream of N₂. The residue was triturated with ether to afford 1.6 g of intermediate 18c as a white solid.



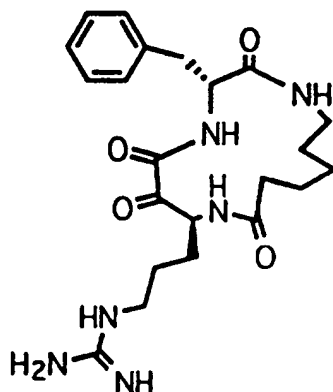
A mixture of intermediate 18c (500 mg, 0.5 mmol), Pd(OH)₂ (600 mg) and methanol (30 mL) was shaken under H₂ at 21 psig for 5 h. The mixture was filtered, and the filtrate was concentrated to afford 390 mg of intermediate 18d as a white solid: m/z 619 (MH⁺).



A solution of intermediate 5 (340 mg, 0.464 mmol) and DMAP (283 mg, 2.32 mmol) in 450 mL of CH₂Cl₂ was treated with BOP-Cl (236 mg, 0.928 mmol) and stirred for 5 h. Solvent was removed under reduced pressure, and the residue was purified via flash column chromatography (silica gel, 95:5 CH₂Cl₂ -MeOH-> 90:10 CH₂Cl₂ -MeOH) to yield 78 mg of intermediate 18e: m/z 601 (MH⁺).



A solution of intermediate **18e** (78 mg, 0.13 mmol) in CH₂Cl₂ (15 mL) was
 5 treated with (82 mg, 0.19 mmol) of the Dess-Martin periodinane. The mixture
 was stirred for 3.5 h, treated with of aqueous 4:1 NaHCO₃-Na₂S₂O₃ (20mL).
 This mixture was extracted four times with 25 mL portions of CH₂Cl₂. The
 combined CH₂Cl₂ extracts were washed with brine, dried (Na₂SO₄), and
 concentrated to provide 49 mg of intermediate **18f** which was used in the
 10 following step without further purification: m/z 599 (MH⁺).



N-[3-(3-BENZYL-2,5,6,9-TETRAOXO-1,4,8-TRIAZACYCLOTETRADEC-
 7-YL)PROPYL]GUANIDINE TRIFLUOROACETIC ACID

15

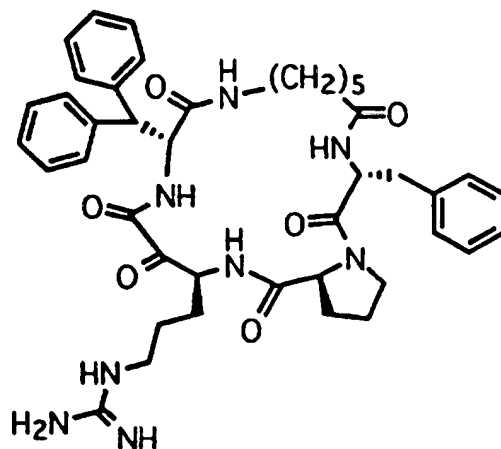
COMPOUND 18

A suspension of intermediate **18f** (49 mg) in anisole (1 mL) was treated with ca.
 5 mL of anhydrous HF at -78 °C. The mixture was stirred at 0 °C for 3.5 h and
 the excess HF was removed under vacuum. The residue was triturated with
 ether and purified by reverse-phase HPLC (MeCN-water-TFA, 30:70:0.2) to give
 20 10.4 mg of the title compound as a white solid: m/z 445 (MH⁺); Anal. Calcd for
 C₂₂H₃₂N₆O₄•1.75C₂HF₃O₂•1.18H₂O:

Calculated: C, 46.03; H, 5.47; N, 12.63; H₂O, 3.19

Found: C, 46.03; H, 4.95; N, 12.99; H₂O, 3.49.

EXAMPLE 19



5R,15R,19S,21AS-N-[3-(15-BENZHYDRYL-5-BENZYL-4,7,14,17,18,21-
HEXAOXODOCOSAHYDRO-3a,6,13,16,20-
PENTAAZACYCLOPENTACYCLOEICOSEN-19-YL)PROPYL]GUANIDINE
TRIFLUOROACETIC ACID
COMPOUND 19

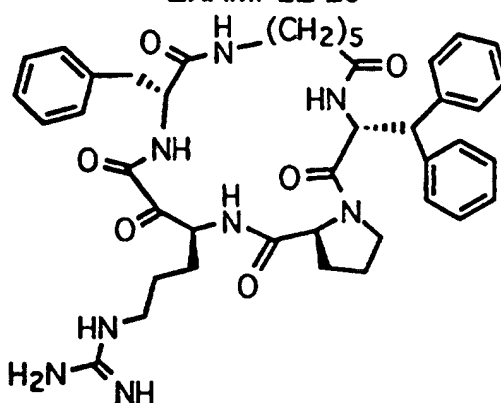
Compound 19 was prepared using the method of Example 11 with the following modifications. 6-Aminohexanoic acid is used in place of 5-aminoheptanoic acid in step 11a and CBZ-D-Phe is replaced with CBZ-D-diPhe (prepared via the method of US Pat 5,198,548) in step 11b to give the title compound as a solid:

FAB-MS m/z 766 (MH⁺); Anal. Calc'd for C₄₂H₅₂N₈O₆•1.75 C₂HF₃O₂•2.25 H₂O:

Calc'd: C, 54.38; H, 5.84; N, 11.15; H₂O, 4.03.

Found: C, 54.57; H, 5.71; N, 11.29; H₂O, 4.09.

EXAMPLE 20



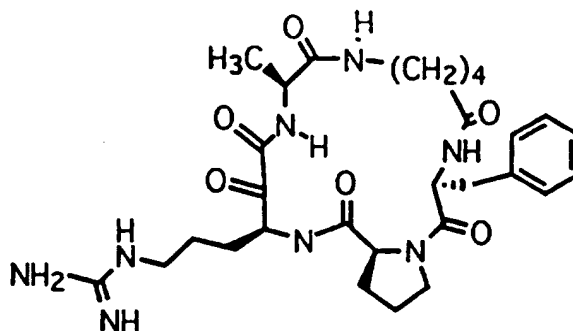
5R,15S,19S,21aS-N-[3-(5,15-DIBENZYL-4,7,14,17,18,21-
HEXAOXODOCOSAHYDRO-3a,6,13,16,20-
PENTAAZACYCLOPENTACYCLOEICOSEN-
19-YL)PROPYL]GUANIDINE TRIFLUOROACETIC ACID
COMPOUND 20

Compound 20 was prepared using the method of Example 11 with the following modifications. 6-Aminohexanoic acid is used in place of 5-aminoheptanoic acid in step 11a and CBZ-D-diPhe-ProO-t-Bu replaced with D-Phe-ProO-t-Bu in step 11d to give the title compound as a solid: FAB-MS m/z 766 (MH^+); Anal. Calc'd for $C_{42}H_{52}N_8O_6 \cdot 2.0 C_2HF_3O_2 \cdot 2.75 H_2O$:

Calc'd: C, 53.00; H, 5.75; N, 10.75; H_2O , 4.75.

Found: C, 53.30; H, 5.51; N, 10.70; H_2O , 4.96.

EXAMPLE 21



5R,14R,18S,20aS-N-[3-(5-BENZYL-14-METHYL-4,7,13,16,17,20-
HEXAOXOEICOSAHYDRO-3a,6,12,15,19-PENTAAZACYCLOPENTA-
CYCLONONADECEN-18-YL)PROPYL]GUANIDINE TRIFLUOROACETIC ACID
COMPOUND 21

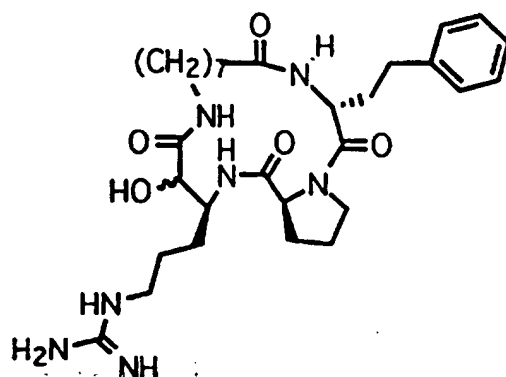
Compound 21 was prepared using the method of Example 11 with the following modifications. 6-Aminohexanoic acid is used in place of 5-aminoheptanoic acid

in step 11a and CBZ-D-Phe is replaced with CBZ-D-Ala in step 11b to give the title compound as a solid: FAB-MS m/z 600 (MH^+); Anal. Calc'd for $C_{29}H_{42}N_8O_6 \cdot 2.15 C_2HF_3O_2 \cdot 2.50 H_2O$:

Calc'd: C, 45.00; H, 5.57; N, 12.16; H_2O , 5.07.

5 Found: C, 45.01; H, 5.46; N, 12.82; H_2O , 5.31.

EXAMPLE 22



10 [20aR-(20aR, 5R, 18S)]-N-[3-(5-PHENYLETHYL-17-HYDROXY-
4, 7, 16, 20-TETRAOXOEICOSAHYDRO-3a, 6, 15, 19-TETRA-
AZACYCLONONADECANE-18-YL) PROPYL] GUANIDINE
COMPOUND 22

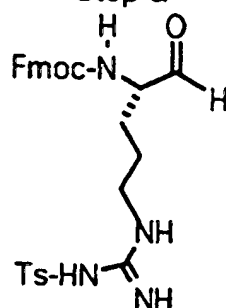
A suspension of intermediate 1h (0.245 g, 0.372 mmol) anisole (2 mL)
15 was cooled to $-78^{\circ}C$ and treated anhydrous HF (ca. 10mL) using a standard HF
apparatus. After stirring for 4 h, HF was removed under reduced pressure at
 $0^{\circ}C$, and the residue was triturated twice with 25 mL portions of ether. The solid
was collected, washed with ether, then purified by reverse-phase HPLC
(MeCN-water-TFA, 30:70:0.2). Lyophilization of the eluate provided the title
20 compound as a white solid : FAB-MS m/z 586 (MH^+); Anal. Calc'd for
 $C_{30}H_{47}N_7O_5 \cdot 2C_2HF_3O_2 \cdot 0.75 H_2O$:

Calc'd: C, 49.36; H, 6.15; N, 11.85; H_2O , 1.63.

Found: C, 49.10, H, 6.07; N, 12.15; H_2O ; 1.42.

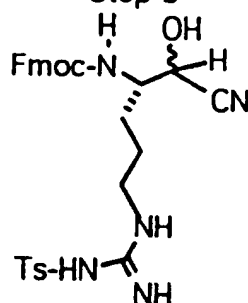
EXAMPLE 23

Step a

**23a**

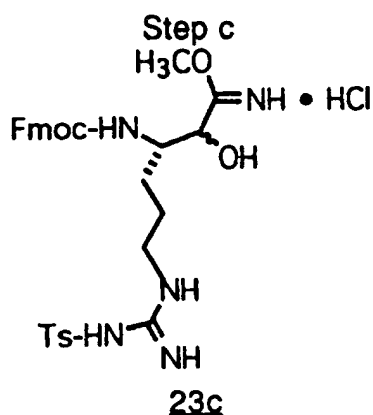
- 5 1,1-Carbonyldiimidazole (1.8 g, 11.0 mmol) was added to a solution of N-α-Fmoc-Nε-tosyl-L-arginine (6.0 g, 10.0 mmol) in anhydrous THF (30 mL) at 0 °C under argon and stirred at 0 °C for 1.5 h. The reaction mixture was cooled to -48 °C and 1M DIBAL (28 mL, 28 mmol) was added dropwise over 20 min. The resulting mixture was stirred for another 1.5 h and 1.2 N HCL (67 mL) was
- 10 added with stirring. The mixture was allowed to warm up to room temperature and partitioned between 0.6N HCl (65 mL) and chloroform. The resulting aqueous layer was washed with several portions of chloroform. The combined organic extracts were washed with successive portions of water and brine, dried (Na₂SO₄) and concentrated in vacuo to afford the aldehyde **23a** as a white
- 15 flakey solid.

Step b

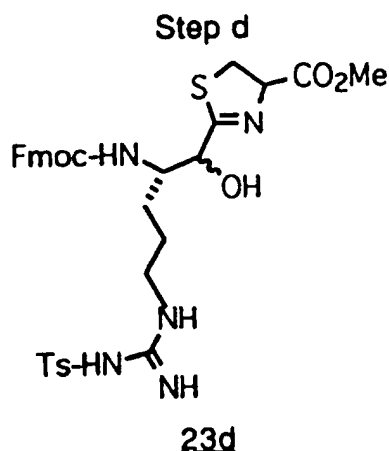
**23b**

- 20 A solution of KCN (1.44 g, 22 mmol) and H₂O (125 mL) was added to a solution of aldehyde **23a** (5.9 g, 11.0 mmol) in ethyl acetate (250 mL) and the resulting mixture was stirred for 40 h at room temperature under argon. The organic layer was separated and the aqueous layer was washed with three portions of ethyl acetate. The combined ethyl acetate extracts were washed with brine,
- 25 dried (Na₂SO₄), concentrated in vacuo and stored in the refrigerator under argon. The residue was partitioned between ethyl acetate (100 mL) and saturated aqueous NaHCO₃ (200 mL) and the pH was maintained at 7.0 by the

addition of solid NaHCO_3 . The solid NaHCO_3 was removed by filtration and the resulting aqueous layer was washed with several portions of ethyl acetate. The combined organic layer was washed twice with brine, dried (MgSO_4) and concentrated in vacuo to give the cyanohydrin 23b as a white solid; FAB-MS m/z 562 (MH^+).



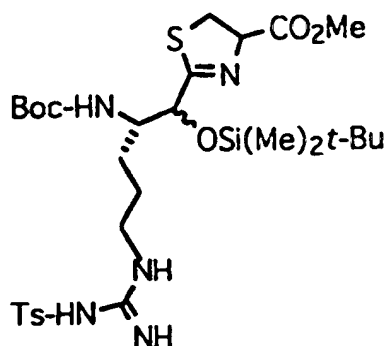
- 10 HCl (21 g) was bubbled into a solution of nitrile 23b (3.0 g, 5.34 mmol) and methanol (53 mL) under argon at a temperature of less than -40°C over 20 min. The reaction vessel was closed under nitrogen and placed in a freezer at -15°C for 46 h and concentrated in vacuo at room temperature. The residue was partitioned between saturated aqueous NaHCO_3 solution (250 mL) and
- 15 ethyl acetate. The organic layer was washed with two portions of brine, dried (MgSO_4) and concentrated in vacuo to give the imidate 23c as a solid.



20

Cysteine methyl ester hydrochloride (2.7 g, 15.9 mmol) was added to a solution of imidate 23c (5.0 g, 7.9 mmol) and CH_2Cl_2 (100 mL) and the resulting mixture was stirred under argon at room temperature for 2 d. The mixture was washed sequentially with brine and water, then dried (Na_2SO_4) and concentrated. The

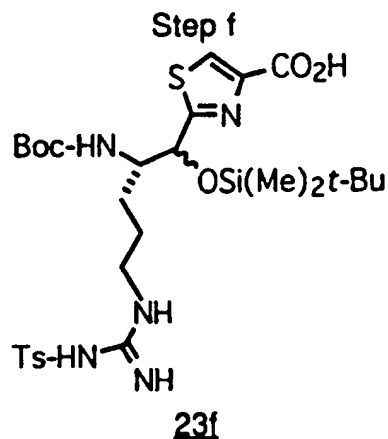
residue was purified by flash chromatography (silica gel, 95:5 CH₂Cl₂-MeOH) to give 3.8 g of **23d** as a white foam: MS m/z 680 (MH⁺).



5

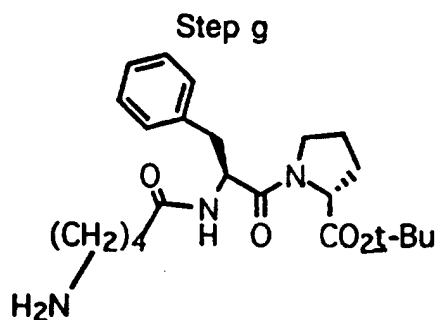
23e

- t*-Butyldimethylsilyltriflate (3.3 g, 12.6 mmol) was added dropwise to a solution of **23d** (1.9 g, 2.8 mmol) and 2,6-lutidine and cooled to 0 °C. The mixture was stirred for 1 h at 0 °C, then quenched with ice. The CH₂Cl₂ layer was washed with water, dried (Na₂SO₄) and concentrated to give the corresponding silyl ether which was used without purification: m/z 794 (MH⁺). The silyl ether was dissolved in 50 mL of 20 % diethylamine -CH₃CN and stirred for 2.5 h. The solution was concentrated, and the residue was purified via flash chromatography (silica gel, CH₂Cl₂->10% MeOH-CH₂Cl₂) to yield 1 g (1.85 mmol) of the corresponding α -amino derivative as an oil. This material (1.0 g, 1.85 mmol) was dissolved in CH₂Cl₂ (25 mL) and treated with di-*t*-butyl dicarbonate (0.49 g, 2.25 mmol) at 0 °C. After stirring overnight at room temperature the reaction was washed with water and the CH₂Cl₂ layer was dried (Na₂SO₄) and concentrated. The residue was purified by flash chromatography (silica gel, 95:5 CH₂Cl₂-MeOH) to afford 1.1 g of **23e** as a semi-solid: m/z 558 (MH⁺).



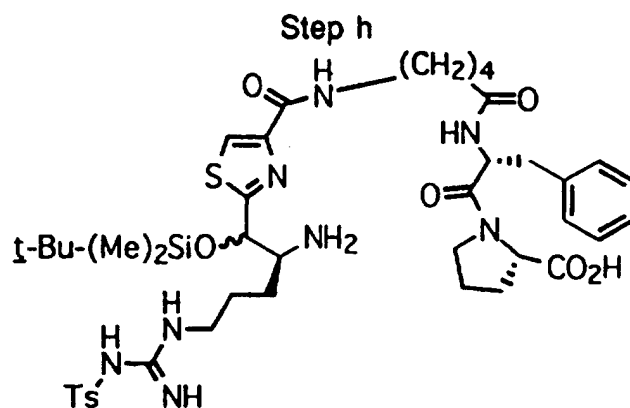
Activated MnO_2 (3.5 g) was added to a solution of **23e** (1.1 g, 1.7 mmol) in CH_2Cl_2 (100 mL). The mixture was stirred for 6.5 h and filtered through dicalite. The filtrate was concentrated, and the residue was purified by flash column chromatography (silica gel; 95:5 CH_2Cl_2 -MeOH) to afford 800 mg (1.3 mmol) of the corresponding thiazole derivative as a white foam. The material was combined with LiOH (94 mg, 3.9 mmol) and 9:1 dioxane-water solution (12 mL). The mixture was stirred for 4 h, diluted with water and acidified to pH 5 with acetic acid. The mixture was extracted three times with ethyl acetate, dried (Na_2SO_4) and concentrated to give **23f** as a white semi-solid: m/z 656 (MH+).

10



Intermediate **23g** was prepared from D-Phe, ProO-t-Bu and 4-(N-carbobenzoxyl)aminobutanoic acid, using steps a-d of Example 1.

15

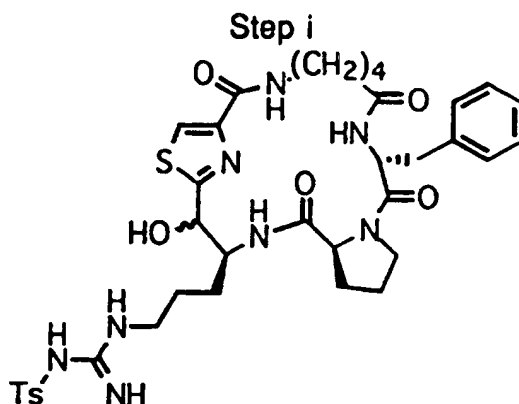


A solution of intermediate **23f** (0.4 g, 0.60 mmol), intermediate **23g** (0.26 g, 0.63 mmol), and HOBt (121 mg, 0.90 mmol) in CH_3CN (10 mL) was treated with DCC (130 mg, 0.63 mmol) in CH_3CN (2 mL). The mixture was stirred overnight, filtered and concentrated. The residue was dissolved in CH_2Cl_2 , washed sequentially with saturated aqueous NaHCO_3 , dried (Na_2SO_4) and concentrated. The residue was purified via flash column chromatography (silica gel, 95:5 CH_2Cl_2 -MeOH) to afford 350 mg of the coupled product as a white

20

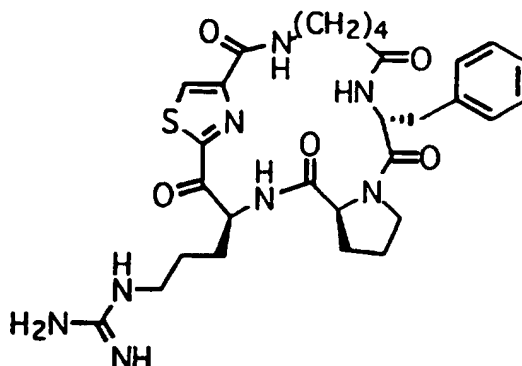
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foam: m/z 1055 (MH^+). The material was dissolved in CH_2Cl_2 (10 mL) and treated with a solution of 1:1 TFA- CH_2Cl_2 (10 mL) at 0 °C. The mixture was stirred for 1 h at room temperature and concentrated under a stream of N_2 at room temperature. The residue was triturated with ether to give 413 mg of intermediate 23h as a white solid: MS m/z 899 (MH^+).



- 10 A solution of intermediate 23h (1.0 g, 0.90 mmol) in CH_2Cl_2 (900 mL) was treated with DMAP (560 mg, 4.6 mmol) followed by BOP-Cl (450 mg, 1.8 mmol). The mixture was stirred for 2 h and concentrated in vacuo. The residue was purified via flash column chromatography (silica gel, 95:5 CH_2Cl_2 -MeOH) to give 500 mg of an off-white solid: m/z 882 (MH^+). This solid was stirred for 1 h
- 15 in 1M Bu_4NF/THF and concentrated under reduced pressure. The residue dissolved in CH_2Cl_2 and washed repeatedly with H_2O . The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to yield 275 mg of the corresponding alcohol 23i which was used in the following step without further purification: m/z 767 (MH^+).

20



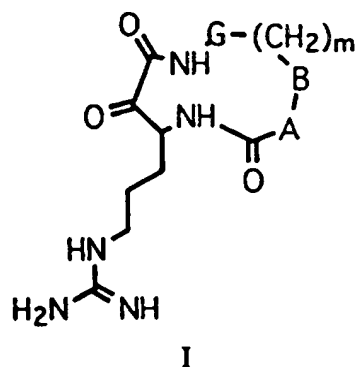
3S,6S,12R-N-[3-(12-BENZYL-2, 5,11,14,20-PENTAOXO-23-THIA-4,10,13,19,24-PENTAAZATRICYCLO[19.2.1.3]-6, 10-TETRACOSA-1(2H), 21-DIEN-3-YL)PROPYL]GUANIDINE

COMPOUND 23

- The alcohol (275 mg) was suspended in 30 mL of CH_2Cl_2 and added to a suspension of the Dess-Martin periodinane (228 mg, 0.54 mmol) in 1 mL of CH_2Cl_2 . The mixture was stirred for 3h, quenched with 25% $\text{Na}_2\text{S}_2\text{O}_3$ (aq) in
- 5 NaHCO_3 (sat'd., aq.) and stirred for 0.5 h. The layers were separated, and the CH_2Cl_2 layer was washed twice with water, dried (Na_2SO_4) and concentrated under reduced pressure to yield 273 mg of the corresponding keto-amide derivative as a foam: m/z 611 (MH^+). A mixture of 270 mg of the keto-amide derivative was suspended in 2 mL of anisole and treated with excess (ca. 10 mL)
- 10 anhydrous HF at -78°C . The mixture was stirred at 0°C for 4.5 h, then HF was removed at 0°C under reduced pressure. The residue was triturated with ether and purified by reverse-phase HPLC (70:30:0.2 H_2O - CH_3CN -TFA). Lyophilization of the eluate provided 120 mg of the title compound as a white solid: FAB-MS m/z 556 (MH^+); Anal. Calc'd for $\text{C}_{29}\text{H}_{38}\text{N}_8\text{O}_5\text{S}\cdot 1.75\text{C}_2\text{HF}_3\text{O}_2\cdot 1.5$
- 15 H_2O :
- | | |
|---------|---|
| Calc'd: | C, 46.62; H, 5.15; N, 13.38, H_2O , 3.23. |
| Found: | C, 46.40; H, 5.03; N, 13.57; H_2O ; 3.33. |

What is claimed is:

1. A compound of the Formula I

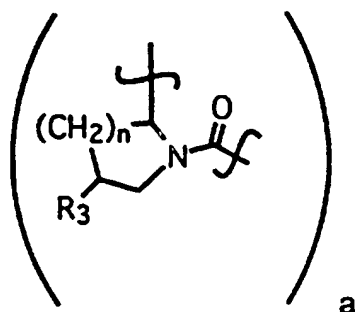


wherein:

m is 2 to 12;

10

A is



15

where the amido carbonyl is bound to B and the α aminomethine is bound to the depicted ring carbonyl,

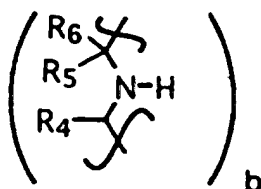
R_3 is hydrogen, hydroxy or C_{1-5} alkoxy,

n is 1 or 2, and

20

a is 0 or 1;

B is



where the amido carbonyl of B is bound to the depicted ring methylene and the methine is bound to A,

5

R₄ is independently selected from the group consisting of hydrogen, C₁₋₅alkyl, carboxyC₁₋₅alkyl, phenyl, substituted phenyl (where the phenyl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine), phenylC₁₋₅alkyl, substituted phenylC₁₋₅alkyl (where the phenyl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine), 3-pyridylC₁₋₅alkyl, 4-pyridylC₁₋₅alkyl, diphenylC₁₋₂alkyl, and naphthyl, substituted naphthyl (where the naphthyl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine),

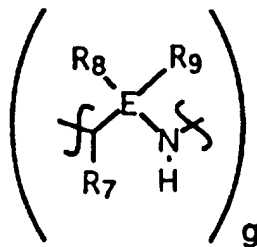
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R₅ and R₆ are hydrogen or taken together with the carbon of attachment to form a carbonyl, and

25

b is 0 or 1;

G is



where the amine of G is bound to the ring methylene and the methine is bound to the depicted amide,

5 R₇ is independently selected from the group consisting of hydrogen, C₁₋₅alkyl, carboxyC₁₋₅alkyl, phenyl, substituted phenyl (where the phenyl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine), phenylC₁₋₅alkyl, substituted phenylC₁₋₅alkyl
10 (where the phenyl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine), 3-pyridylC₁₋₅alkyl, 4-pyridylC₁₋₅alkyl, diphenylC₁₋₂alkyl, and naphthyl, substituted naphthyl (where
15 the naphthyl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine),

20 E is carbon or C(CH₂)_q, where q is 0 to 12, with the proviso that the sum of q and m cannot exceed 25,

R₈ and R₉ are hydrogen or taken together with the carbon of E to form a carbonyl, and

25 g is 0 or 1;

or the pharmaceutically acceptable salt thereof.

- 30 2. The compound of Claim 1 where a is 1, b is 0 and g is 0.
3. The compound of Claim 2 where n is 1.
4. The compound of Claim 1 where a is 0, b is 1 and g is 0.
5. The compound of Claim 4 where R₅ and R₆ are taken together with the carbon to which each is attached to form a carbonyl, and
35 R₄ is selected from the group consisting of phenyl, substituted phenyl (where the phenyl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine),

- phenylC₁₋₅alkyl, substituted phenylC₁₋₅alkyl (where the phenyl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine), diphenylC₁₋₂alkyl, naphthyl and substituted naphthyl (where the aryl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine).
6. The compound of Claim 1 where a is 0, b is 0 and g is 1.
- 10 7. The compound of Claim 6 where E is carbon, R₈ and R₉ are taken with the carbon of attachment for form a carbonyl, and R₇ is selected form the group consisting of phenyl, substituted phenyl (where the phenyl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine), phenylC₁₋₅alkyl, substituted phenylC₁₋₅alkyl (where the phenyl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine), diphenylC₁₋₂alkyl, naphthyl and substituted naphthyl (where the aryl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine).
8. The compound of Claim 6 where R₈ and R₉ are hydrogen, E is C(CH₂)_q and q is 0-6.
9. The compound of Claim 1 where a is 1, b is 1 and g is 0.
10. The compound of Claim 9 where n is 1, R₅ and R₆ are taken together with the carbon of attachment to form a carbonyl, and R₄ is selected form the group consisting of phenyl, substituted phenyl (where the phenyl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine), phenylC₁₋₅alkyl, substituted phenylC₁₋₅alkyl (where the phenyl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine), diphenylC₁₋₂alkyl, naphthyl and substituted naphthyl (where the aryl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino,

hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine).

11. The compound of Claim 1 where a is 1, b is 1 and g is 1.
- 5 12. The compound of Claim 11 where n is 1, R₅ and R₆ are taken together with the carbon of attachment to form a carbonyl, and
R₄ is selected from the group consisting of phenyl, substituted phenyl (where the phenyl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine), phenylC₁₋₅alkyl, substituted phenylC₁₋₅alkyl (where the phenyl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine), diphenylC₁₋₂alkyl, naphthyl and substituted naphthyl (where the aryl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine),
10 E is carbon,
15 R₈ and R₉ are taken with the carbon of attachment to form a carbonyl, and
20 R₇ is selected from the group consisting of phenyl, substituted phenyl (where the phenyl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine), phenylC₁₋₅alkyl, substituted phenylC₁₋₅alkyl (where the phenyl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine), diphenylC₁₋₂alkyl, naphthyl and substituted naphthyl (where the aryl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine).
25 30
35 13. The compound of Claim 11 where n is 1, R₅ and R₆ are taken together with the carbon of attachment to form a carbonyl, and
R₄ is selected from the group consisting of phenyl, substituted phenyl (where the phenyl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy,

- 5 C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine), phenylC₁₋₅alkyl, substituted phenylC₁₋₅alkyl (where the phenyl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine), diphenylC₁₋₂alkyl, naphthyl and substituted naphthyl (where the aryl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine),
- 10 R₈ and R₉ are hydrogen, E is C(CH₂)_q, and q is 0-6.
14. The compound of Claim 1 where a is 1, b is 0 and g is 1.
- 15 15. The compound of Claim 14 where n is 1, E is carbon, R₈ and R₉ are taken with the carbon of attachment for form a carbonyl, and R₇ is selected form the group consisting of phenyl, substituted phenyl (where the phenyl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine), phenylC₁₋₅alkyl, substituted phenylC₁₋₅alkyl (where the phenyl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine), diphenylC₁₋₂alkyl, naphthyl and substituted naphthyl (where the aryl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine).
- 25 16. The compound of Claim 14 where n is 1, R₈ and R₉ are hydrogen, E is C(CH₂)_q and q is 0-6.
- 30 17. The compound of Claim 1 where a is 0, b is 1 and g is 1.
18. The compound of Claim 17 where R₅ and R₆ are taken together with the carbon of attachment to form a carbonyl, and R₄ is selected form the group consisting of phenyl, substituted phenyl (where the phenyl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine), phenylC₁₋₅alkyl, substituted phenylC₁₋₅alkyl (where the phenyl
- 35

substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine), diphenylC₁₋₂alkyl, naphthyl and substituted naphthyl (where the aryl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine);

E is carbon,

R₈ and R₉ are taken with the carbon of attachment for form a carbonyl, and

R₇ is selected from the group consisting of phenyl, substituted phenyl (where the phenyl substituents are C₁₋₅alkyl, carboxy

C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine),

phenylC₁₋₅alkyl, substituted phenylC₁₋₅alkyl (where the phenyl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine), diphenylC₁₋₂alkyl, naphthyl and substituted naphthyl (where the aryl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine).

19. The compound of Claim 11 where R₅ and R₆ are taken together with the carbon of attachment to form a carbonyl, and

R₄ is selected from the group consisting of phenyl, substituted phenyl (where the phenyl substituents are C₁₋₅alkyl, carboxy

C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine),

phenylC₁₋₅alkyl, substituted phenylC₁₋₅alkyl (where the phenyl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine), diphenylC₁₋₂alkyl, naphthyl and substituted naphthyl (where the aryl substituents are C₁₋₅alkyl,

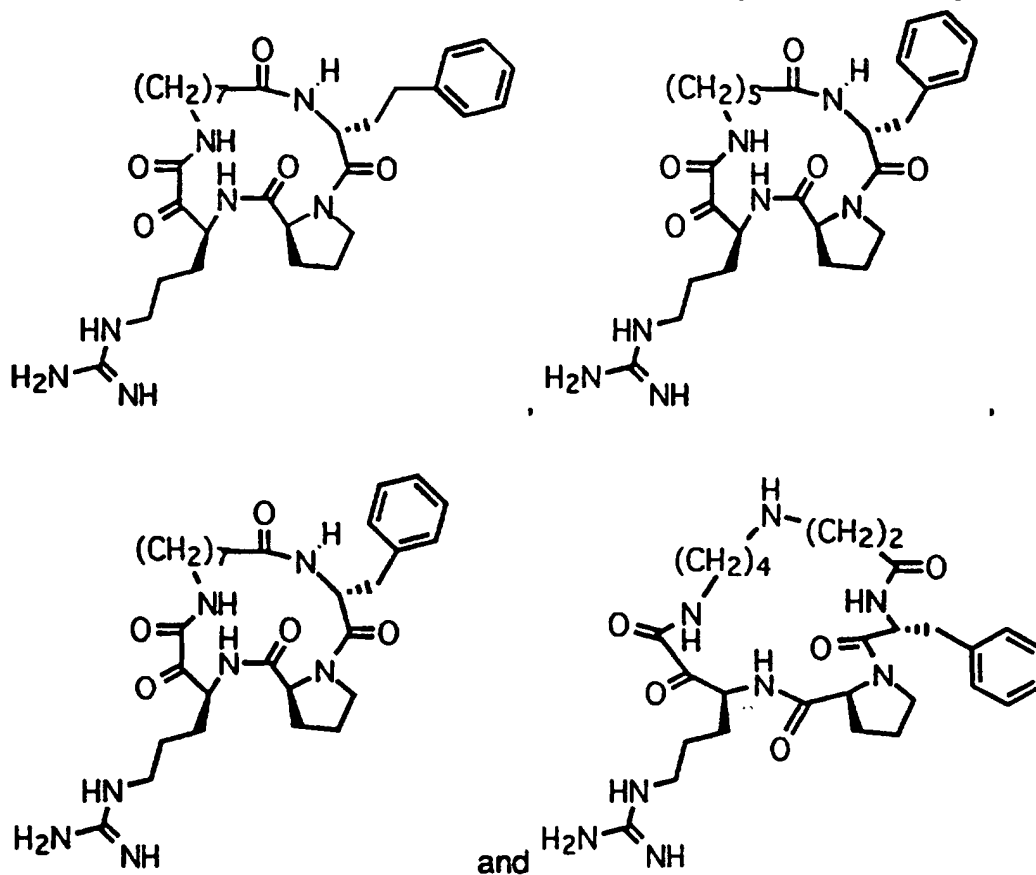
carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine)

R₈ and R₉ are hydrogen,

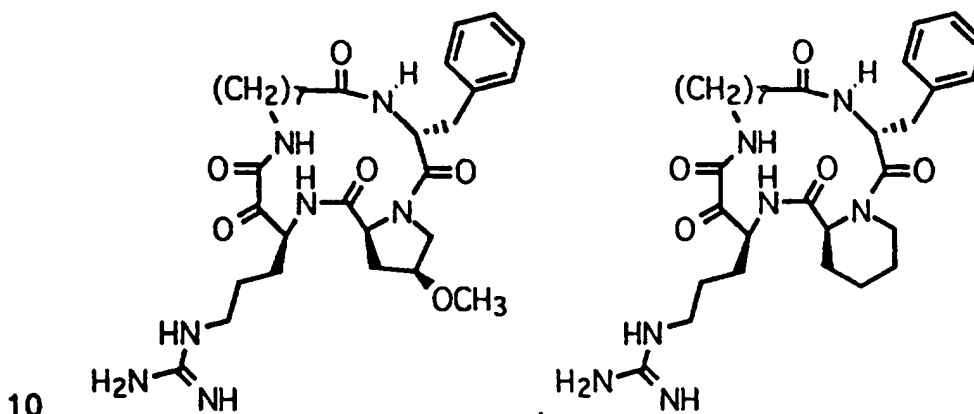
E is C(CH₂)_q, and

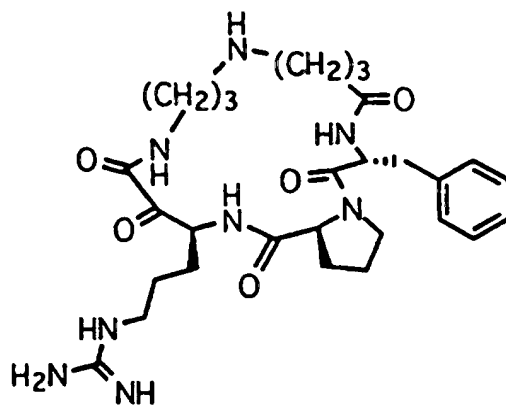
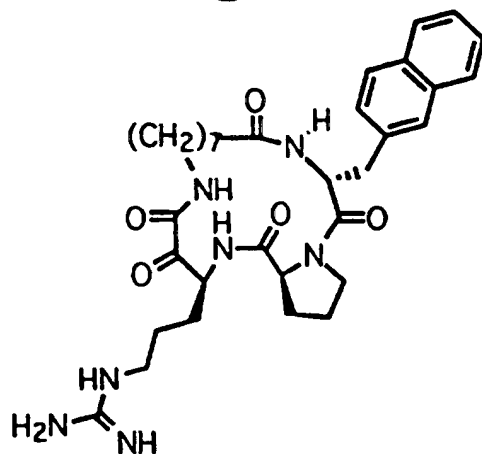
q is 0-6

20. The compounds of Claim 1 selected from the group consisting of

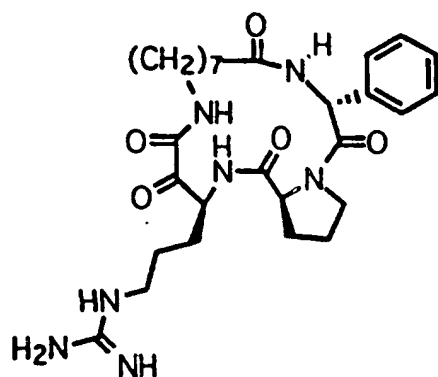


21. The compounds of Claim 1 selected from the group consisting of

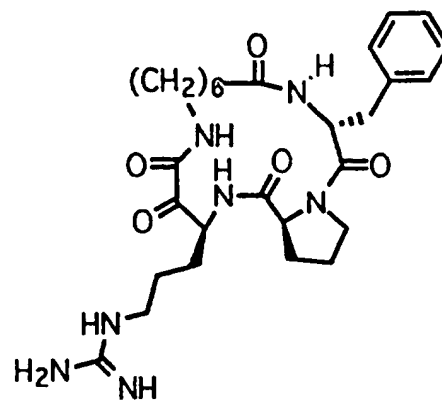
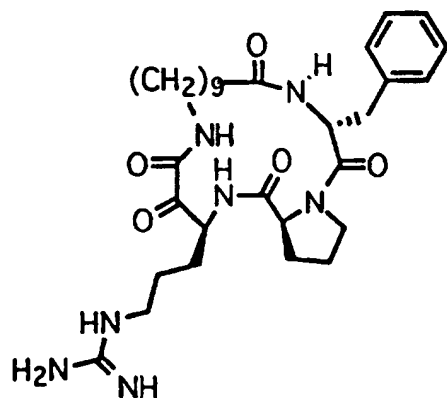


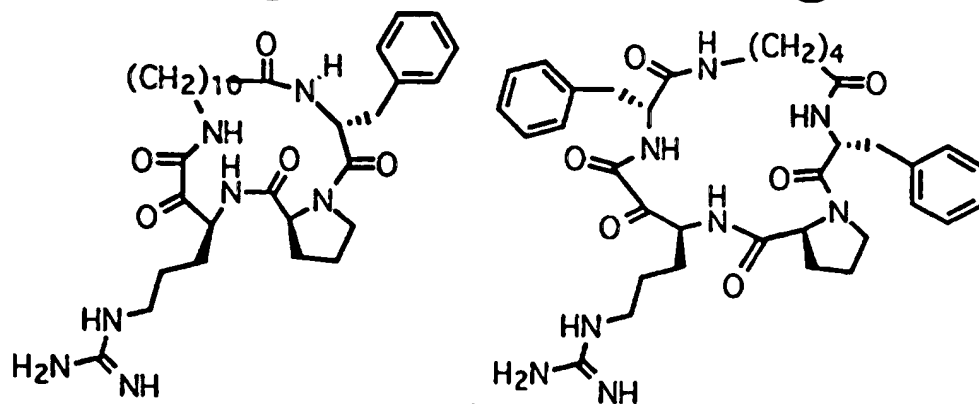


and

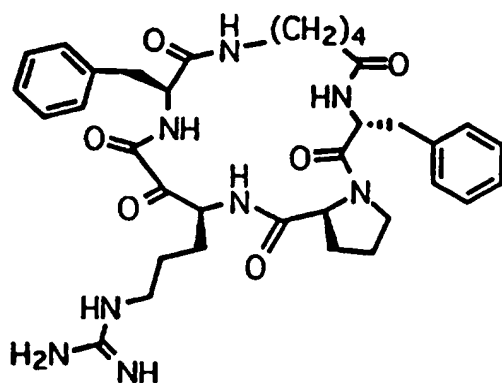


5 22. The compounds of Claim 1 selected from the group consisting of

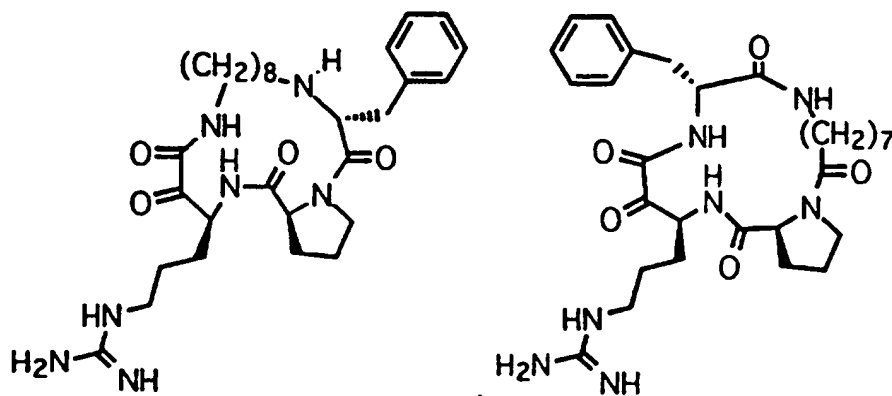


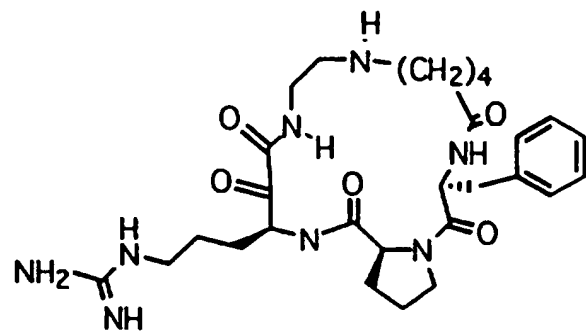
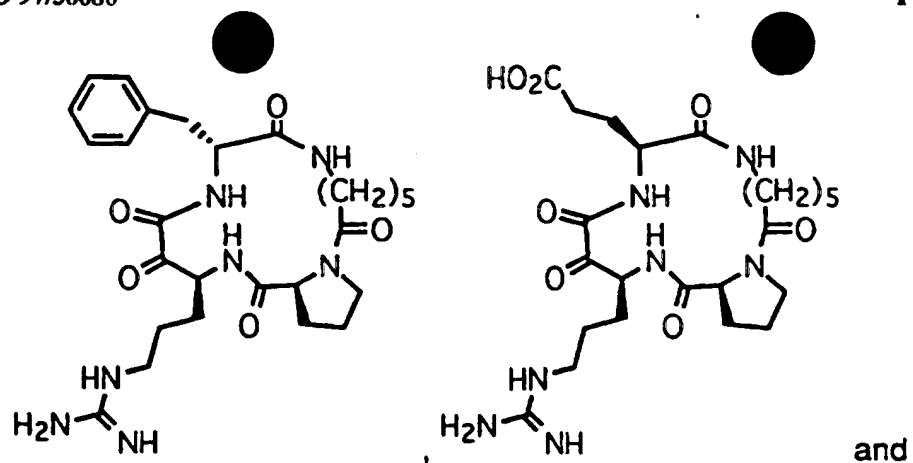


and

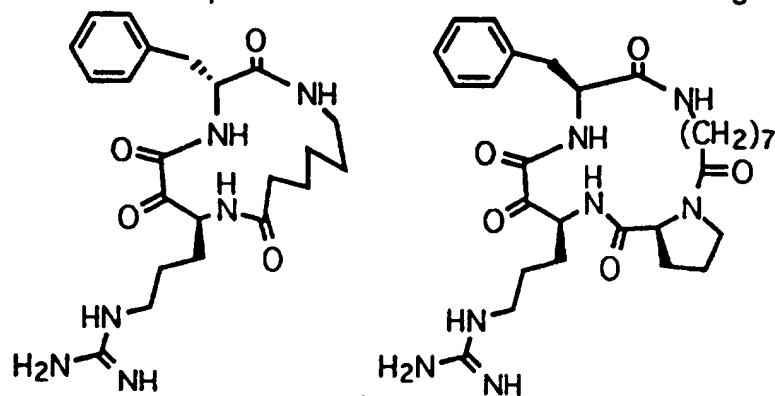


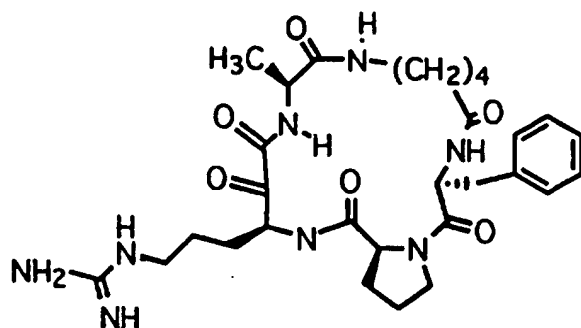
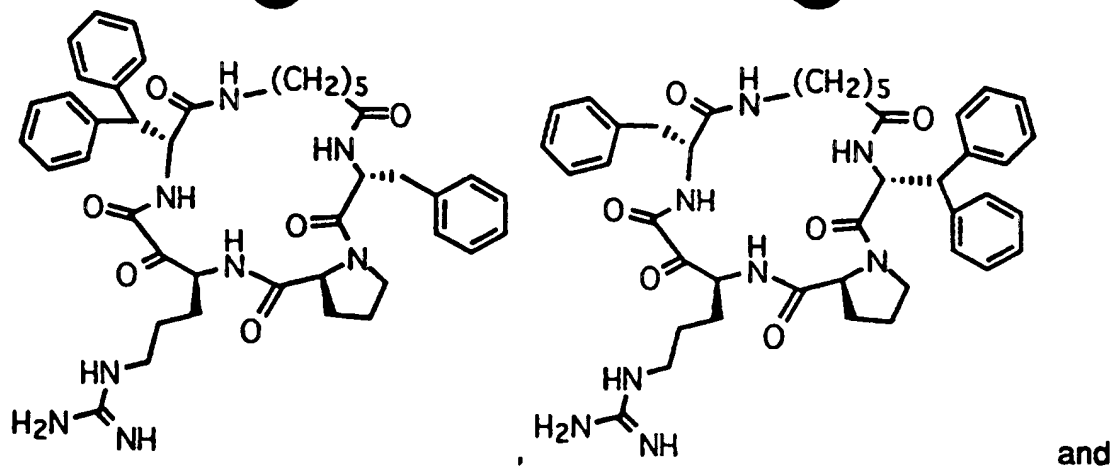
- 5 23. The compounds of Claim 1 selected from the group consisting of



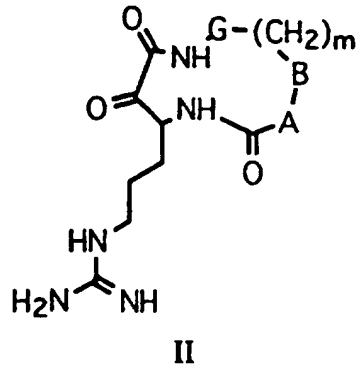


5 24. The compounds of Claim 1 selected from the group consisting of





5 25. A compound of the Formula II



wherein:

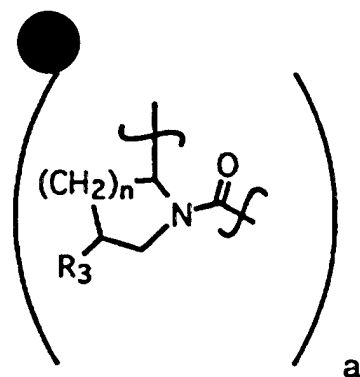
R₁ is hydroxy;

10

R₂ is hydrogen;

m is 2 to 12;

15 A is



where the amido carbonyl is bound to B and the α aminomethine is bound to the depicted ring carbonyl,

5

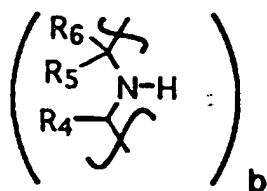
R_3 is hydrogen or C_{1-5} alkoxy,

n is 1 or 2, and

10

a is 0 or 1;

B is



15

where the amido carbonyl of B is bound to the depicted ring methylenes and the methine is bound to A,

20

R_4 is independently selected from the group consisting of hydrogen, C_{1-5} alkyl, carboxy C_{1-5} alkyl, phenyl, substituted phenyl (where the phenyl substituents are C_{1-5} alkyl, carboxy C_{1-5} alkoxycarbonyl, carboxamido, amino, C_{1-5} alkylamino, hydroxy, C_{1-5} alkylcarbonylamino, C_{1-5} alkoxy, fluorine bromine or chlorine), phenyl C_{1-5} alkyl, substituted phenyl C_{1-5} alkyl (where the phenyl substituents are C_{1-5} alkyl, carboxy C_{1-5} alkoxycarbonyl, carboxamido, amino, C_{1-5} alkylamino, hydroxy, C_{1-5} alkylcarbonylamino, C_{1-5} alkoxy, fluorine bromine or chlorine), 3-pyridyl C_{1-5} alkyl, 4-pyridyl C_{1-5} alkyl, diphenyl C_{1-2} alkyl, and naphthyl, substituted naphthyl (where the naphthyl substituents are C_{1-5} alkyl, carboxy

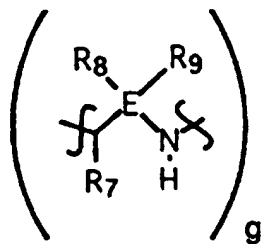
25

C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine),

5 R₅ and R₆ are hydrogen or taken together with the carbon of attachment to form a carbonyl, and

b is 0 or 1;

10 G is



where the amine of G is bound to the ring methylenes and the methine is bound to the depicted amide,

15

R₇ is independently selected from the group consisting of hydrogen, C₁₋₅alkyl, carboxyC₁₋₅alkyl, phenyl, substituted phenyl (where the phenyl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine), phenylC₁₋₅alkyl, substituted phenylC₁₋₅alkyl (where the phenyl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine), 3-pyridylC₁₋₅alkyl, 4-pyridylC₁₋₅alkyl, diphenylC₁₋₂alkyl, and naphthyl, substituted naphthyl (where the naphthyl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine),

30

E is carbon or C(CH₂)_q, where q is 0 to 12, with the proviso that the sum of q and m cannot exceed 25,

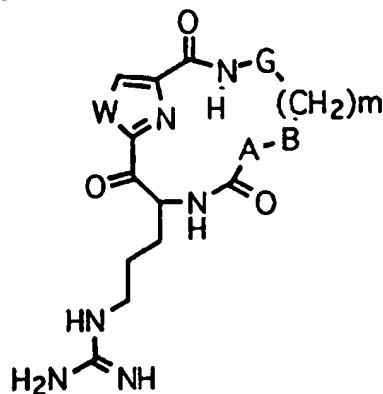
R_8 and R_9 are hydrogen or taken together with the carbon of E to form a carbonyl, and

g is 0 or 1;

5

and pharmaceutically acceptable salts thereof.

26. A compound of the Formula III.



III

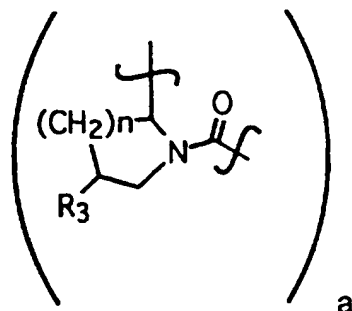
10

wherein:

m is 2 to 12;

15 W is nitrogen, sulfur or oxygen;

A is



20

where the amido carbonyl is bound to B and the α aminomethine is bound to the depicted ring carbonyl,

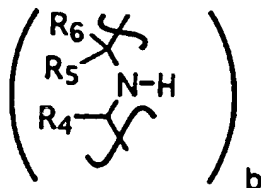
R_3 is hydrogen, hydroxy or C_{1-5} alkoxy,

25

n is 1 or 2, and

a is 0 or 1;

B is



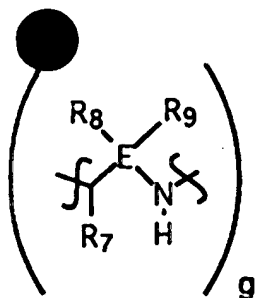
where the amido carbonyl of B is bound to the depicted ring methylene and the methine is bound to A,

R_4 is independently selected from the group consisting of hydrogen, C_{1-5} alkyl, carboxy C_{1-5} alkyl, phenyl, substituted phenyl (where the phenyl substituents are C_{1-5} alkyl, carboxy C_{1-5} alkoxycarbonyl, carboxamido, amino, C_{1-5} alkylamino, hydroxy, C_{1-5} alkylcarbonylamino, C_{1-5} alkoxy, fluorine bromine or chlorine), phenyl C_{1-5} alkyl, substituted phenyl C_{1-5} alkyl (where the phenyl substituents are C_{1-5} alkyl, carboxy C_{1-5} alkoxycarbonyl, carboxamido, amino, C_{1-5} alkylamino, hydroxy, C_{1-5} alkylcarbonylamino, C_{1-5} alkoxy, fluorine bromine or chlorine), 3-pyridyl C_{1-5} alkyl, 4-pyridyl C_{1-5} alkyl, diphenyl C_{1-2} alkyl, and naphthyl, substituted naphthyl (where the naphthyl substituents are C_{1-5} alkyl, carboxy C_{1-5} alkoxycarbonyl, carboxamido, amino, C_{1-5} alkylamino, hydroxy, C_{1-5} alkylcarbonylamino, C_{1-5} alkoxy, fluorine bromine or chlorine);

R_5 and R_6 are hydrogen or taken together with the carbon of attachment to form a carbonyl, and

b is 0 or 1;

G is



where the amine of G is bound to the ring methylene and the methine is bound to the depicted amide,

5

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R₇ is independently selected from the group consisting of hydrogen, C₁₋₅alkyl, carboxyC₁₋₅alkyl, phenyl, substituted phenyl (where the phenyl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine), phenylC₁₋₅alkyl, substituted phenylC₁₋₅alkyl (where the phenyl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine), 3-pyridylC₁₋₅alkyl, 4-pyridylC₁₋₅alkyl, diphenylC₁₋₂alkyl, and naphthyl, substituted naphthyl (where the naphthyl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine),

E is carbon or C(CH₂)_q, where q is 0 to 12, with the proviso that the sum of q and m cannot exceed 25,

25

R₈ and R₉ are hydrogen or taken together with the carbon of E to form a carbonyl, and

g is 0 or 1;

30 and pharmaceutically acceptable salts thereof.

27. The compound of Claim 26 where a is 1, b is 0 and g is 0.

28. The compound of Claim 27 where n is 1.

29. The compound of Claim 26 where a is 0, b is 1 and g is 0.
30. The compound of Claim 29 where R₅ and R₆ are taken together with the carbon of attachment to form a carbonyl, and
R₄ is selected from the group consisting of phenyl, substituted phenyl
(where the phenyl substituents are C₁₋₅alkyl, carboxy
C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy,
C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine),
phenylC₁₋₅alkyl, substituted phenylC₁₋₅alkyl (where the phenyl
substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido,
amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy,
fluorine bromine or chlorine), diphenylC₁₋₂alkyl, naphthyl and
substituted naphthyl (where the aryl substituents are C₁₋₅alkyl,
carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino,
hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or
chlorine).
31. The compound of Claim 26 where a is 0, b is 0 and g is 1.
32. The compound of Claim 31 where E is carbon, R₈ and R₉ are taken with the carbon of attachment to form a carbonyl, and
R₇ is selected from the group consisting of phenyl, substituted phenyl
(where the phenyl substituents are C₁₋₅alkyl, carboxy
C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy,
C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine),
phenylC₁₋₅alkyl, substituted phenylC₁₋₅alkyl (where the phenyl
substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido,
amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy,
fluorine bromine or chlorine), diphenylC₁₋₂alkyl, naphthyl and
substituted naphthyl (where the aryl substituents are C₁₋₅alkyl,
carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino,
hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or
chlorine).
33. The compound of Claim 31 where R₈ and R₉ are hydrogen, E is C(CH₂)_q and q is 0-6.
34. The compound of Claim 26 where a is 1, b is 1 and g is 0.
35. The compound of Claim 34 where n is 1, R₅ and R₆ are taken together with the carbon of attachment to form a carbonyl, and
R₄ is selected from the group consisting of phenyl, substituted phenyl
(where the phenyl substituents are C₁₋₅alkyl, carboxy
C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy,

C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine), phenylC₁₋₅alkyl, substituted phenylC₁₋₅alkyl (where the phenyl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine), diphenylC₁₋₂alkyl, naphthyl and substituted naphthyl (where the aryl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine).

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36. The compound of Claim 26 where a is 1, b is 1 and g is 1.

37. The compound of Claim 36 where n is 1, R₅ and R₆ are taken together with the carbon of attachment to form a carbonyl, and

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R₄ is selected from the group consisting of phenyl, substituted phenyl (where the phenyl substituents are C₁₋₅alkyl, carboxy

C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine),

20

phenylC₁₋₅alkyl, substituted phenylC₁₋₅alkyl (where the phenyl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine), diphenylC₁₋₂alkyl, naphthyl and substituted naphthyl (where the aryl substituents are C₁₋₅alkyl,

25

carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine),

E is carbon,

R₈ and R₉ are taken with the carbon of attachment to form a carbonyl, and

30

R₇ is selected from the group consisting of phenyl, substituted phenyl (where the phenyl substituents are C₁₋₅alkyl, carboxy

C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine),

35

phenylC₁₋₅alkyl, substituted phenylC₁₋₅alkyl (where the phenyl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine), diphenylC₁₋₂alkyl, naphthyl and substituted naphthyl (where the aryl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino,

hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine).

38. The compound of Claim 36 where n is 1, R₅ and R₆ are taken together with the carbon of attachment to form a carbonyl; and

5 R₄ is selected from the group consisting of phenyl, substituted phenyl (where the phenyl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine), phenylC₁₋₅alkyl, substituted phenylC₁₋₅alkyl (where the phenyl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine), diphenylC₁₋₂alkyl, naphthyl and substituted naphthyl (where the aryl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine),
10 R₈ and R₉ are hydrogen,
E is C(CH₂)_q, and
q is 0-6.

- 20 39. The compound of Claim 26 where a is 1, b is 0 and g is 1.

40. The compound of Claim 39 where n is 1, E is carbon, R₈ and R₉ are taken with the carbon of attachment for form a carbonyl, and

25 R₇ is selected from the group consisting of phenyl, substituted phenyl (where the phenyl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine), phenylC₁₋₅alkyl, substituted phenylC₁₋₅alkyl (where the phenyl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine), diphenylC₁₋₂alkyl, naphthyl and substituted naphthyl (where the aryl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine),
30
35

41. The compound of Claim 39 where n is 1, R₈ and R₉ are hydrogen, E is C(CH₂)_q and q is 0-6.

42. The compound of Claim 26 where a is 0, b is 1 and g is 1.

43. The compound of Claim 42 where R₅ and R₆ are taken together with the carbon of attachment to form a carbonyl, and

R₄ is selected from the group consisting of phenyl, substituted phenyl (where the phenyl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine), phenylC₁₋₅alkyl, substituted phenylC₁₋₅alkyl (where the phenyl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine), diphenylC₁₋₂alkyl, naphthyl and substituted naphthyl (where the aryl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine),

E is carbon,

R₈ and R₉ are taken with the carbon of attachment to form a carbonyl, and

R₇ is selected from the group consisting of phenyl, substituted phenyl (where the phenyl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine), phenylC₁₋₅alkyl, substituted phenylC₁₋₅alkyl (where the phenyl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine), diphenylC₁₋₂alkyl, naphthyl and substituted naphthyl (where the aryl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine).

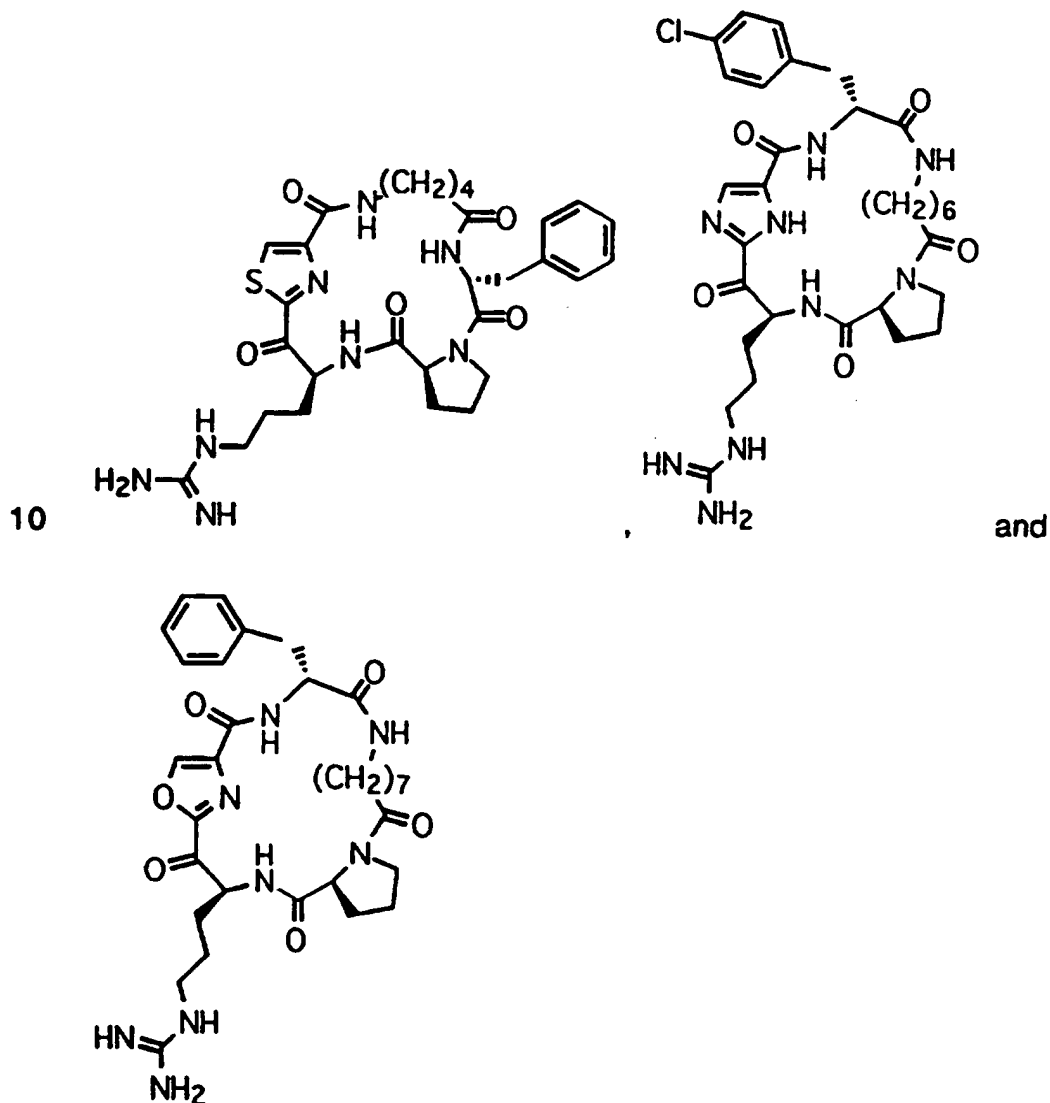
44. The compound of Claim 42 where R₅ and R₆ are taken together with the carbon of attachment to form a carbonyl and

R₄ is selected from the group consisting of phenyl, substituted phenyl (where the phenyl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine), phenylC₁₋₅alkyl, substituted phenylC₁₋₅alkyl (where the phenyl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine).

fluorine bromine or chlorine), diphenylC₁₋₂alkyl, naphthyl and substituted naphthyl (where the aryl substituents are C₁₋₅alkyl, carboxy C₁₋₅alkoxycarbonyl, carboxamido, amino, C₁₋₅alkylamino, hydroxy, C₁₋₅alkylcarbonylamino, C₁₋₅alkoxy, fluorine bromine or chlorine);

R₈ and R₉ are hydrogen, E is C(CH₂)_q and q is 0-6

45. The compounds of Claim 26 selected from the group consisting of



46. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective amount of a compound of Claim 1 or of Claim 26 for treating thrombin mediated diseases in a mammal.

47. A method for inhibiting thrombin comprising contacting a compound of Claim 1 or of Claim 26 with a medium containing thrombin.
48. The method of Claim 47 where the compound contacts the medium via
5 an orthopedic or a surgical device.
49. The method of claim 47 where the medium is mammalian blood.
50. A method of claim 49 where the mammal is a human.
10
51. A method treating a thrombin mediated disease in a mammal comprising administering an effective amount of a compound of Claim 1 or of Claim 26.
52. A method for inhibiting trypsin comprising contacting a compound of Claim 1 or of Claim 26 with a medium containing trypsin.
15
53. A method of treating a trypsin related disorder in a mammal comprising administering an effective amount of a compound of Claim 1 or of Claim 26.
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INTERNATIONAL SEARCH REPORT

International Application No
US 97/02575A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07K7/56 C07K5/12 C07K5/06 C07K5/02 A61K38/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	BIOORG. MED. CHEM., vol. 3, no. 8, 1995, pages 1025-1038, XP000654364 MARYANOFF, B.E. ET AL.: "Cyclotheonamide derivatives: ..."	
A	J. AM. CHEM. SOC., vol. 117, 1995, pages 1225-1239, XP000652221 MARYANOFF, B.E. ET AL.: "Macrocyclic peptide inhibitors of serine proteases ..."	
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Date of the actual completion of the international search

8 July 1997

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

International Application No

P 97/02575

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	<p>BIORG. MED. CHEM. LETTERS, vol. 6, no. 24, 1996, pages 2947-2952, XP000654183 GRECO, M.N. ET AL.: "Novel thrombin inhibitors that are based on a macrocyclic tripeptide motif" * Table 1; page 2950 *</p> <p style="text-align: center;">-----</p>	<p>1-25, 47-53</p>

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